MARCO TOIA

**ON CLINICAL AND MECHANICAL
ASPECTS OF IMPLANT-SUPPORTED
SCREW-RETAINED MULTI-UNIT
CAD-CAM METAL FRAMEWORK**

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IMPLANT-SUPPORTED SCREW-RETAINED MULTI-UNIT
CAD-CAM METAL FRAMEWORK

Malmö University
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Malmö University, 2020
Faculty of Odontology
Department of Oral and Maxillofacial Surgery
and Oral Medicine
Malmö, Sweden

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To the greatest dad, dentist, friend, husband.

To the greatest man I have ever met.

To my father Sandro.

This thesis is number 55 in a series of investigations on implants, hard tissues and the locomotor apparatus originating from the Department of Biomaterials, University of Gothenburg, the Department of Prosthetic Dentistry/Material Sciences and the Department of Oral & Maxillofacial Surgery and Oral Medicine, Malmö University.

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THESIS AT A GLANCE

Study	Aim	Illustration	Key Findings
(I) Effect of Misfit at Implant-Level Framework and Supporting Bone on Internal Connection Implants: Mechanical and Finite Element Analysis.	To assess the effects of misfit at IL FPDs and supporting bone level on the generation of implant cracks with a coupled method of a mechanical test and FEA.		Implant fracture is a rare event. Effective stresses greater than fatigue limit were noticed when the misfit was present. The crack is more likely to occur when implants are fully supported by marginal bone compared with a bone loss scenario.
(II) Influence Implant vs abutment level connection in implant supported screw-retained fixed partial dentures with cobalt-chrome framework: 1-year interim results of a randomized clinical study.	To evaluate MBL change and clinical parameters when implants are restored with a screw-retained FPD in an IL or AL setup after 1-year of follow-up.		A low grade of MBL was present after 1 year. IL showed greater amount of MBL and soft tissue inflammation indexes than AL. In FPD, AL may be a safer procedure than IL setup in order to preserve a healthy periimplant tissue.
(III) Fixed full-arch maxillary prostheses supported by four versus six endosseous implants with titanium CAD/CAM milled framework: 3-year multicentre RCT.	To evaluate MBL change and clinical parameters between the 4-I and 6-I group after 3-year of function in the rehabilitation of the edentulous maxilla with a screw retained FCD.		FCDs supported by 4 and 6 implants did not show any difference in MBL and clinical parameters. Fractures and chipping of the veneers components were the most reported complications.
(IV) Patient satisfaction and clinical outcomes in implant-supported overdentures retained by milled bars: Two-year follow-up.	To evaluate patient centred outcomes in subjects treated with rigid anchored IODs and to evaluate clinical parameters.		Rigid anchored IODs lead to patients' satisfaction regarding aesthetics and mastication function. No significant difference in MBL change was noted at the follow-up visit.

ABSTRACT

Conventionally casted frameworks have been considered the preferred solutions for complete and partial restorations since the beginning of implantology. However, following technological development, the computer aided design/computer aided manufacturing (CAD-CAM) with milling the frameworks has been introduced as an alternative option with the potential of minimising inaccuracies, reducing the operator dependence and offering a homogeneous structure with high mechanical properties. The CAD-CAM multi-unit reconstruction varies with fixation type, implant framework connection, and prostheses material. However, the materials developed for the use of CAD-CAM, may have different technical and biological complications with time.

The present thesis aims to provide insights into the risk of complications in screw-retained multi-unit frameworks manufactured using the CAD-CAM technique.

An *in vitro* test (**Study I**) was performed to assess the effects of misfit at implant-level FPDs and supporting bone levels on the generation of implant cracks. Three clinical studies were conducted: in **Study II**, partially edentulous patients were rehabilitated with either an abutment or implant level multi-unit Cobalt-Chromium metal-ceramic framework; in **Study III**, patients, edentulous in the maxilla, were treated with either four or six implants and rehabilitated with a fixed titanium metal-acrylic framework; in **Study IV** edentulous patients were treated with removable overdentures retained by titanium milled bars. In **Study III** and **IV**, Oral Health Related Quality of Life was evaluated.

The marginal bone level change was clinically not significant regardless of fixation type (**Study II**), retention (**Study III-IV**), and material used (**Study II-III-IV**). No framework complications were registered. Patients reported a high level of satisfaction after the treatment (**Study III-IV**).

Based on the studies included in this thesis, the following conclusions can be made: (i) the risk of implant cracks in screw-retained Implant Level (IL) Fixed Partial Denture (FPD) is low, even with a misfit; (ii) according to the 1-year data presented in **Study II**, abutment level (AL) retention is recommended for FPDs; (iii) the cost-effective for a maxillary Fixed Complete Denture (FCD) supported by four implants can be considered predictable and comparable to six implants; (iv) implant-supported FCDs and Implant supported Over-Dentures (IOD) are associated with high rates of patient satisfaction, related to aesthetics and mastication function mainly resulting from the high stability of the prostheses; (v) the technical and biological complications reported in FPDs, FCDs and IODs were limited. However, a considerable percentage of prosthetic fractures and chippings were reported for FCDs at 1-year and 3-year follow-ups. Clinicians have to be aware that additional visits may be required for maintaining the prostheses.

LIST OF PAPERS

The dissertation is based on four papers, which will be referred to in the main text by their Roman numerals. The papers are appended at the end of the thesis.

- I. Effect of Misfit at Implant-Level Framework and Supporting Bone on Internal Connection Implants: Mechanical and Finite Element Analysis.
Toia M, Stocchero M, Jinno Y, Wennerberg A, Becktor JP, Jimbo R and Halldin A.
The International Journal of Oral & Maxillofacial Implants. 2019;34(2):320-328.
- II. Influence Implant vs abutment level connection in implant supported screw-retained fixed partial dentures with cobalt-chrome framework: 1-year interim results of a randomized clinical study.
Toia M, Stocchero M, Becktor JP, Chrcanovic B, Wennerberg A.
Clinical Implant Dental and Related Research. 2019;21(2):238-246.
- III. Fixed full-arch maxillary prostheses supported by four versus six endosseous implants with titanium CAD-CAM milled framework: 3-year multicentre RCT.
Toia M, Stocchero M, Corrà E, Becktor JP, Wennerberg A, Cecchinato D.
Clinical Oral Implant Research 2020 (accepted)

- IV. Patient satisfaction and clinical outcomes in implant-supported overdentures retained by milled bars: Two-year follow-up.

Toia M, Wennerberg A, Torrisi P, Farina V, Corrà E, Cecchinato D.

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Contribution by the respondent

The respondent performed most of the work from planning to the experimental work (with the exception of the FEA analysis) and the majority of the data analyses. The respondent was the main contributor to the writing of all the manuscripts.

ABBREVIATIONS

4-I	Four Implants
6-I	Six Implants
AL	Abutment Level
AM	Additive Manufacturing
Au	Gold
BIC	Bone-to-Implant-Contact
BG	Bone Gain
BL	Base-Line time point (final prostheses delivery)
BoP	Bleeding on Probing
CAD-CAM	Computer-Aided Design-Computer-Aided Manufacturing
CD	Conventional Denture
CNC	Computer Numeric Controlled
Co-Cr	Cobalt Chromium
FCD	Implant supported Fixed Complete Denture
FEA	Finite Element Analysis
FPD	Implant supported Fixed Partial Denture
IAC	Implant Abutment Connection
ICC	Internal Conical Connection
IL	Implant Level
IOD	Implant supported OverDenture

IP	Implant Placement
ITV	Insertion Torque Value
KM	Keratinised Mucosa
L&Z	Lekholm and Zarb classification
MBL	Marginal Bone Level
MITT	Modified Intention-To-Treat analysis
N	Newton
OHIP	Oral Health Impact Profile
OHRQoL	Oral Health-Related Quality of Life
PI	Plaque Index
PPD	Probing Pocket Depth
PROM	Patient Reported Outcome Measure
PT	Pre-Treatment
SM	Subtractive Manufacturing
S-N	Stress and number of cycles
Ti	Titanium
UCLA	Universal Clearance Limited Abutment
UTS	Ultimate Tensile Strength
Zi	Zirconia

INTRODUCTION

Long-term follow-ups support the use of osseointegrated implants for the rehabilitation of patients with different types of edentulism¹⁻¹¹. However, technical and biological complications are still reported regardless of the high implant survival rates^{7,12,13}.

These clinical complications were reported at a 33.6% incidence for implant-supported Fixed Partial Dentures (FPD) after five years; one out of three patients experienced some problems over a medium-term period¹⁴. Other analyses focusing on the implant-supported Fixed Complete Dentures (FCD) reported 29.3% and 8.6% ‘prostheses free of complications’ after 5 and 10 years, respectively¹⁵.

One of the main critical aspects of these high rates of complications is that they affect not only the patient’s satisfaction, but also the total cost for maintenance and the supplementary costs for dental care providers^{16,17}.

One of the aspects to consider is the relation between clinicians’ iatrogenic procedures and the complications¹⁸. Jemt and Stenport¹⁹ reported that the most publications belonging from universities originated from ‘specialist teams’, with remarkable experience of treating implant patients.

However, regardless of the clinician’s willingness to follow the recommended clinical protocols rigidly^{2,20}, it is not uncommon for patients to have complications with triggers that cannot be attributed to any reported risk factors. Possible alterations in the patient’s immune-regulatory system may interfere with the inflammatory mechanism of defence, leading the implant steady-state condition to a total breakdown²¹. Apart from the biochemical role that guides the bone tissue formation around implants^{20,22-24}, restorations have

to handle not only the hard and soft tissue reaction but also the parafunctional activities that may damage the prosthetic rehabilitation at different levels.

The implant-prostheses were, as reported by the original protocol², screw-retained with Au-alloy casted frameworks representing the most proper solution for complete, partial and single-unit restorations.

Within the last two decades, several manufacturing techniques have been introduced for fabricating frameworks²⁵ and the need for further research on superstructure materials for the FCD, especially for the upper jaw, has been addressed²⁶.

Moreover, it was noted, by Albrektsson and Donos²⁷, that the shape of the framework is crucial for the survival rates of implant-supported fixed dental prostheses.

Even if a certain degree of misfit was reported to be clinically acceptable²⁸, highly accurate prosthetic procedures are recommended, to limit critical misfit conditions, mainly when different screw-retained FPD setups were chosen²⁹.

In 1999, Jemt et al.³⁰ proposed the computer numeric-controlled (CNC) milled method as an alternative to the conventional casted framework. This revolutionary technique could minimise inaccuracies, reduce operator dependency and offer a homogeneous structure with high mechanical properties. The computer aided design computer aided manufacturing (CAD-CAM) technology is now widely used in many types of procedures, mainly customised, with different materials for framework production or for prostheses/veneering purposes. However, these newly introduced materials, with the plethora of options available, may present different technical and biological complications overtime³¹.

In this thesis, the technical and biological complications of screw-retained multi-unit rehabilitations using CAD-CAM milled metal frameworks, with different implant-abutment connections and different retention methods, are evaluated.

OSSEOINTEGRATION PROCESS

Oral rehabilitation with dental implants may be considered the gold standard when one or more teeth are lost. Successful dental implants can withstand masticatory forces since they are firmly anchored to the residual ridge bone. The predictability of such treatment is based on a solid scientific background. Modern dental implant research has been flourishing since the global acceptance of the ‘osseointegration’, a term coined by professor P.I. Brånemark³² to indicate the Bone-to-Implant-Contact (BIC) at a microscopic level. An independent group, led by professor Schroeder³³, referred to this phenomenon as ‘functional ankylosis’ and firstly demonstrated ‘osseointegration’ using histological analyses.

Successful osseointegration is obtained at the interface where direct contact between the living bone and the load-bearing implant occurs without the presence of fibrous tissue, and can be observed with light microscopy^{20,34}.

An osseointegrated dental implant is a medical device inserted into the human jawbone, which has gradually been surrounded by healthy hard and soft tissues without provoking an extensive inflammatory host response. This beneficial biomaterial-host interaction, however, has important prerequisites. The osseointegration process depends on six precise parameters: (i) implant material, (ii) implant design, (iii) implant surface characterisation, (iv) bone aspect, (v) surgical procedure, and (vi) loading condition during the healing time²⁰.

Nowadays, it is acknowledged that the long-term success of dental implants depends on the health of: (i) the bone crestal and supra-crestal peri-implant tissues at the time of the surgery, and (ii) the prosthetic connection, both across the entire lifetime of the

restoration. As defined by Zarb and Albrektsson³⁵, osseointegration is *‘a process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading.’*

Healing of the bone compartment

When an implant is inserted into an osteotomy, the first bone-to-implant interface is established. Vascularisation is interrupted and the bone activates signals that enhance the healing process. Osteoclasts are activated from a quiescent stage and osteoblasts derived from the mesenchymal stem cells begin to deposit an osteon matrix. This initial mechanical contact between the implant and bone tissue is subjected to continuous modification, driven by interlaced biomechanical and biological mechanisms throughout the healing and functioning periods.

Implant stability is considered one of the most important factors for a successful osseointegration³⁶. Initial implant mechanical anchorage to the bone is known as primary stability. The gradual bone remodelling during the first two weeks on the implant surface in the empty chambers among threads by de novo bone formation^{37,38} or the interfacial remodelling of the pre-existing bone, depending on the contact between the implant body and the bone tissue, provides the secondary (or biological) stability^{39,40}.

The remodelling process consists of five phases: (i) activation, (ii) resorption, (iii) reversal, (iv) formation, (v) termination. Although this process may be influenced by several factors such as patient conditions, implant characteristics (micro-macro design and stability) and the surgical technique, 17 weeks are reported as the required time for a complete remodelling process during implant placement in humans⁴¹.

After osseointegration, the prosthetic suprastructure is attached to the implants. It is reported that the first year of loading is considered as an adaptation period characterised by peri-implant bone adsorption of the share strain and stress distribution, which dynamically modifies the quality and quantity compositions and dimensions according to the stimuli^{2,42}.

Healing of the supra-crestal compartment

The organisation of the supra-crestal tissue, comprising of connective tissue and an epithelium layer, in an appropriate vertical dimension is gradual and takes several weeks. In an *in vivo* study⁴³ and a human study⁴⁴, it was reported that the connective fibres and the epithelium layer were organised within 4-6 and 6-8 weeks, respectively. Moreover, in a human experiment, inflammatory cells were observed in the connective layer up to 12 weeks after implant placement⁴⁴.

The height of the supra-crestal barrier from the bone crest to the apical portion of the peri-implant mucosa had an average of 3.65 ± 0.44 mm; this was established by Berglundh and Lindhe⁴⁵. The authors performed a study on beagle dogs and reported that the junctional epithelium had vertical dimension between 2.0 and 2.1 mm while the connective layer varied between 1.3 ± 0.3 mm and 1.8 ± 0.4 mm. Similar findings were also reported by other authors^{46,47}.

Moon et al.⁴⁸ explained the composition of the peri-implant attached connective tissue. A 40 μ m area that faced the abutment consists of abundant fibroblast cells within the collagen fibres and no blood vessels, while within a distance of 160 μ m, fewer fibroblasts and more collagen fibres and blood vessels were present. A previous report was different; the connective layer was described to be deficient in cells and vascular structures, but rich in collagen fibres⁴⁹.

The findings reported by Moon et al. indicated that the supra-crestal compartment, having fibroblast cells, may contribute to a vital seal between the oral environment and the peri-implant bone tissue⁴⁸.

IMPLANT DISTRIBUTION

Fixed Complete Dentures

Since the initial investigation on the treatment of edentulous patients, which was conducted from 1965 to 1980, a period divided into ‘*initial*’, ‘*development*’ and ‘*routine*’², the number of implants needed for a FCD became a topic significant interest and several clinical recommendations were proposed.

Brånemark et al.⁵⁰ conducted a retrospective study on 156 patients treated between 1968 and 1978 with 10 years of follow-up. Four or six implants were placed in both jaws according to the residual anatomical bone condition. Six implants were always the first option if bone volume permitted it. However, if the pristine residual bone presented space for only four implants, this was considered a better option than increasing the number of implants with additional surgery (e.g. bone augmentation). It was stated that, if the minimum residual native bone permitted the installation of four implants, the insertion of more implants was questionable. However, tendencies of lower survival were observed in the patients treated with four instead of six implants⁵¹.

Zarb et al. also addressed the question of the number of implants needed for the rehabilitation of edentulous jaws. In a prospective study of 49 patients who were treated with 274 implants with a follow-up period between 4 to 9 years, the average implant number in each arch was 5.47⁵². The authors described that a ‘*specific formula*’ for determining the number of implants needed to support the occlusal bearing loading capacity and the potential parafunctional activities, was not obtainable. It was also reported that placing more

implants, even if appropriate for specific clinical conditions, could lead to subsequent complications for the prosthetic design.

Three significant factors influenced the debate on the number of implants to be used for the rehabilitation of edentulous patients in the 1980s and 1990s. The first was related to the implant surface characteristics; the second was on the possibility of loading implants immediately; the third was related to installing implants in augmented bones.

Implant surface characteristics

The Branemark implants used in the 'early periods' had a machined surface topography with pure commercial titanium (cpTi) that could lead to early failures up to 10%, more frequently in the maxilla, during the healing process after implant placement^{2,53-57}. This drawback restricted clinicians to install more implants than necessary to successfully guarantee the continuity of the treatment. As an example, Zarb and Schmitt's longitudinal clinical study⁵² reported that after the initial placement of the 268 implants, three of the forty-nine patients lost their implants early and had supplementary implants inserted, ending up with a total number of 274 implants.

In 1981 Albrektsson et al.²⁰, followed by Thomas & Cook in 1985⁵⁸, declared that the implant surface has a significant effect on the prognosis of the implant treatment. Due to significant contribution by Wennerberg^{23,59}, who analysed the details of the different surface characterisations and bone healing, implant companies were able to start producing implants with a roughened surface.

In 1999, Buser et al.⁶⁰ reported that implants with roughened surfaces had the following features: '(i) *a faster bone integration*, (ii) *a higher percentage of BIC and* (iii) *a higher resistance to shear with higher Removal Torque Value (RTV) when compared to machined implants.*'

Immediate loading of implants

The advancements made in the field of osseointegration thanks to the novel implant surfaces, lead clinicians to start loading the implants directly after implant installation. This was done with the ambition to reduce the treatment time and to achieve immediate patient comfort.

However, the immediate loading procedures ignited a debate on the number of implants needed for such treatments.

Primary stability due to implant-bone interlocking is a prerequisite for successful immediate loading. However, two clinical conditions may hamper the stability of the implants: (i) the presence of soft bone in the osteotomy site, particularly the case of the maxilla posterior segments, and (ii) the immediate implant installation in post-extractive sites with limited residual bone ridge availability. When faced with these two conditions, clinicians may be persuaded to install more implants to gain sufficient support for the immediate prosthesis's installation.

During the 1990s, case series were conducted to document the immediate loading procedures⁶¹⁻⁶⁵. The first data reported the risk of losing more implants compared to the conventional two-stage approach. In reaction, clinicians installed up to 13 implants in one jaw in certain cases⁶⁶(Figure 1).

Figure 1. A) Panoramic after implant placement and immediate loading. B) Panoramic after the definitive prostheses⁶⁶.

However, in 1999 Brånemark et al.⁶⁷ proposed the Novum® system, which consisted of a prefabricated surgical guide and prosthetic components for the mandible. This made it possible to immediately load and deliver a final fixed restoration on only 3 implants. Although this was innovative at the time, it was considered too complex, targeted a limited number of patients with a high bone quality, and was soon abandoned⁶⁸.

After these early experiences, the immediate loading technique became a well-established procedure with specific clinical recommendations^{69,70}, even for cases with poor bone quantity and quality^{71,72}.

Implants in augmented bone

Another factor to be considered when planning for prosthetic rehabilitation is the prognosis of implants installed in the augmented bone, especially in the treatment of an edentulous maxilla. The outcomes of grafting the resorbed edentulous jaw with⁷³ or without immediate implant placement⁷⁴ were investigated. The studies showed that the survival rates of the implants in grafted bone, compared to native bone, were inferior^{75,76}.

Thor et al.⁷⁷ reported on 19 patients with reabsorbed maxilla in which an iliac or particulate bone graft and autogenous platelet-rich plasma were used for bone reconstruction. The implants had moderately rough surfaces (TiOblast™, Astra Tech AB, Mölndal, Sweden). At the abutment connection procedure, 2 implants out of 152 (8 implants/patient) were removed, resulting in a survival rate of 98% (Table 31).

In a review from 2009 Lambert et al.⁷⁸ reported that implants with rough surfaces used in augmented bone, had a survival rate comparable to implants placed in native bone. Moreover, the authors observed that implant distribution in the edentulous maxilla had an impact on the implant survival rate. The survival rate was lower in patients if their implants were placed only in the anterior maxillary region and not distributed across the posterior and anterior regions. In addition, the review suggested six implants as optimal for the prosthetic rehabilitation of an edentulous maxilla. However, the authors acknowledged that the scientific evidence to support this statement was weak.

Data from other studies report a risk of increased bone loss and implant failures in augmented areas compared to the native bone during the first year of loading. After this initial period, no remarkable bone alterations or differences were observed^{76,79,80}.

Decrease in the number of implants

A systematic review of the rehabilitation of edentulous patients showed that there was insufficient evidence to determine the accurate number and distribution of implants⁸¹. However, the authors concluded that the use of more than six implants remains questionable, confirming what was reported by P.I. Brånemark in 1995⁵⁰.

From the International Team for Implantology (ITI) consensus meeting held in 2014, it was reported that many options have been explored and documented in literature, because of the high heterogeneity of the edentulous cases, and choices depended on the prosthetic design, varying between a splinting cross-arch rehabilitation option and a segmented concept⁸².

In another systematic review on the outcomes of implants and prostheses in patients rehabilitated with more or fewer than 5 implants, no statistical differences were reported in survival rates regardless of the number of implants used⁸³.

In the last decade, several authors investigated FCDs on a low number of implants following the first experiences with the Brånemark Novum® system^{67,84-86}.

Hatano et al.⁶⁸ retrospectively followed 396 implants installed in the mandibles of 132 patients (3 implants each) and immediately loaded. The survival rates after a mean of 5 years of follow-up were 96.7% and 92.4% for implants and reconstructions, respectively. The authors installed implants with machined and oxidised surfaces and observed a failure rate of 7% and 1.2%, respectively, in the first year.

Oliva, Oliva and Oliva⁸⁷ reported no implant loss in a retrospective trial with 5 years of follow-up involving 17 patients who received 3 implants in each jaw to support 2 FCDs loaded with a conventional two-stage approach.

Recently, in a series of studies, the use of 3, and even 2, immediately loaded implants for the rehabilitation of edentulous maxilla and mandibles was investigated⁸⁸⁻⁹². In a 5-year prospective study of 80

patients who were treated with 160 immediately loaded implants for an FCD mandible, there was a high implant survival rate with only 2 implant failures in the first 3 weeks of loading⁹⁰. Furthermore, in a 3-year prospective randomised clinical trial, 60 patients, edentulous in the mandible, were treated with either 2 or 4 implants, in two clinics. No difference between the implant survival rates of the two groups was reported. However, a statistical difference was observed between bone losses recorded by the two clinics where patients were treated⁹³.

It is also reported that the use of only one implant to support an immediate loading FCD in the mandible was tested. Nevertheless, the authors questioned the usefulness of this procedure⁹⁴.

From the analysis of the current literature, the optimum number of implants could not be determined and a '*one-fits-all*' approach could not be identified since several factors have to be considered depending on the complexity of the entire surgical and prosthetic treatment plan⁸³.

Overdentures

Similar questions have been raised on the optimal number of implants to be used for an overdenture (IOD). Moreover, variable prosthetic anchorages with 1 to 6 implants have been proposed.

In the 1970s, alongside Brånemark's research team, a group from the University of Bern^{33,95} together with a private Swiss research team (Straumann, Waldenburg, Switzerland) developed an implant system called titanium plasma-sprayed (TPS) screw or 'Swiss Screw'. The Swiss group focused on removable dentures retained by implants for the rehabilitation of the edentulous jaw. This differed from the approach of the Swedish clinicians who investigated the FCD.

In 1977, the 'Swiss Screw' was finally named 'ITI® Dental Implant System'. This implant was suitable for the mandibular IOD in patients who were not able to wear conventional dentures. According to the procedure guidelines, four implants were placed in the mandible that had been splinted with a Dolder bar to stabilise the patient's realigned denture⁹⁶. In case the patient's denture was unsuitable for realignment, a new overdenture was fabricated, including bar clips, to arrange for the correct retention.

This treatment was carefully described by Buser et al. in 1988⁹⁷ in a study where 95 implants were inserted in the mandible of 25 edentulous patients. Only 3 implants presented signs of infection after 33 months.

A comparative multicentre study with the aim of evaluating the efficacy of two implants systems to support an IOD was performed between 1984 and 1987. Twenty-five patients (68 implants) in Toronto and 34 patients (74 implants) in Bern were treated with an IOD supported by Brånemark implants (Nobelpharma AB, Gothenburg, Sweden) and ITI Bonefit hollow-cylinder implants (Institut Straumann, Waldenburg, Switzerland), respectively. The majority of patients had 2 implants installed and splinted with a bar. No differences were noted between the two implant systems used, and no implants were lost during the 5 years of follow-up⁹⁸.

In 1988, Engquist et al.⁹⁹ presented a study involving 11 Swedish clinics in the treatment of edentulous patients with IODs supported by an average of 3.8 implants. Both jaws were considered. In the lower jaw, the implant survival rate was 99%, while a high failure rate was reported for the maxilla.

Following the McGill consensus meeting on IODs in 2002, the conventional denture was no longer considered the most appropriate treatment for the purpose of restoring the edentulous mandible. An overdenture supported by a minimum of 2 implants seems to be the most appropriate choice for the treatment of edentulous mandibles¹⁰⁰.

In some cases, only one implant^{101,102} was used to retain a mandibular denture. In a prospective study, a 100% survival rate after 5 years of follow-up in 21 patients treated with an IOD retained by only one implant was reported¹⁰².

In contrast to the mandibular, the maxillary IOD was associated with high implant failure rates^{99,103-106}.

One attribution for this high rate of complications was biased treatment planning. Maxillary IOD, at the beginning of its use, was not chosen as a first option; it was selected as an alternative solution for cases with failed implants, which had been installed to support an FCD^{52,104}.

Another explanation was reported by Jemt et al.¹⁰⁷ in a 5-year prospective multicentre study with cumulative survival rates of 72.4%

and 77.9% for implants and IODs, respectively. The author stated that failure rates were due to the different bone qualities between the maxilla and the mandible. It was also reported that the implants used in the first stage of the trial presented a smooth surface, which could lead to higher failure rates in comparison to a moderately rough surface^{108,109}.

In 2001, Kiener et al. reported on edentulous patients that were treated in the maxilla with an IOD supported by 4 or 6 implants¹¹⁰. After a mean follow-up period of 3.2 years (1-8) the implant survival rates were approximately 95.5%. The authors stated that the higher success rates, different from previous reports^{52,104}, was related to the selection of the IOD as the first treatment option. Moreover, the authors described that splinted implants together with a rigid fixed bar presented a higher implant survival rate than implant-supported single attachments¹¹⁰.

Ferrigno et al.¹⁰⁸ conducted a 10-year follow-up study involving 1286 implants installed for the treatment of the edentulous jaw. The implants placed in the maxilla, supporting an IOD, were splinted with a Dolder bar and the 6-implant modality had a higher cumulative success rate (92.2%) compared to the 4-implant (86.9%).

In another 5-year prospective multicentre study, high implant survival rates in patients treated with four implants splinted with a Dolder bar were reported. The survival rates for the maxilla and mandible were 97.4% and 98.6%, respectively¹¹¹. Slot et al.¹¹² reported no differences in failures and complications when 4 or 6 splinted implants were used for the rehabilitation of the edentulous maxilla with IODs after a 5-year follow-up in two studies using two different implant systems. The authors reported a survival rate of 100% for the 4-implant group and 99.2% for the 6-implant group in one study and 100% for the 4-implant group and 99.5% for the 6-implant group in the second clinical trial¹¹³.

In a review that evaluated protocols for maxillary IODs, it was reported that 4 implants were recommended for optimal support. If less than 4 implants were used, a splinted rigid bar was the best solution for reducing implant failures¹⁰⁹.

Fixed Partial Dentures

Following the experience of Brånemark's protocol for the treatment of edentulism, partial and single edentulism began to be treated with implants for fixed restorations¹¹⁴. A combination of teeth and implants as abutments was initially proposed^{115,116}. However, this might compromise the integrity of the tooth structure and potentially lead to additional problems¹¹⁷. Consequently, the use of just implants, as abutments to support FPDs, was proposed and first analysed in a preliminary study¹¹⁸ and, subsequently, in prospective studies^{119,120}.

The partial edentulous segments may present with various grades of resorptions of the alveolar bone and more complications to anatomical limitations, such as the maxillary sinus region and the inferior alveolar nerve in the mandible¹²¹.

Regarding the number to be used for partial reconstructions, 2, 3, and 4 implants were used to support FDPs¹¹⁹.

After 5 years of service, a clinical study reported a significantly higher screw loosening in FPDs with fewer implants compared to those with a higher number of implants. The survival rate was 97.7% for prostheses and 98.4% for loaded implants with a bone loss of 0.8 mm (± 0.6 mm)¹²².

In 2004, Weenström et al. published a 5-year prospective study involving 51 patients who were treated with 149 implants installed in both jaws. Fifty-six FPDs were placed and they were subdivided; 22, 32, and 2 were supported by 2, 3, and 4 implants, respectively. The authors reported three FPDs each were lost due to implant loss, had screw loosening, and had minor chipping of the ceramic, respectively. Total failure rates after 5 years were 5.9% at the subject level and 5.3% at prostheses level. The mean bone level change after 5 years was 0.41 mm.

It can be concluded that at least 2 implants are needed for FPD as support for a 3-unit bridge⁸¹.

Tilted implants

An implant that diverges from its trajectory perpendicularly to the occlusal plane is defined as a 'tilted implant'; however, a precise definition does not exist¹²³. Usually the 'tilting' is assessed as a bi-dimensional mesiodistal inclination from the occlusal plane on an X-ray vision.

In a meta-analysis published by Chrcanovic et al.¹²⁴, it was reported that there were no differences in survival rates and bone losses between axially or non-axially positioned implants.

The first patients treated in the history of the implantology⁵¹ received implants placed perpendicularly to the occlusal plane in areas with sufficient bone. As a consequence, in patients with reduced amount of bone available in the posterior areas, implants were often installed in the more anterior regions, leaving the final prosthesis was constructed with extensive cantilevers to offer a good chewing capacity.

To avoid the cantilever-related risk of fracturing implants and/or their components, alternative options were proposed: (i) shortened prosthetic dental arch^{52,125} (ii) bone augmentation procedures to permit the placement of an adequate numbers of implants^{73-75,126,127}. Interestingly, Adell et al.² had already proposed the installation of some angulated implants (n=6) in the region of the mental foramina or the anterior walls of the maxillary sinus in the early '80s (Figure 2).

Figure 2. 'Maxillary fixtures after 6 years of bridge function. Note the close relation of the oblique fixture to the anterior wall of the maxillary sinus'².

In 1988, the ITI Bonefit implant system designed, specifically for the maxillary region close to the sinus area, a 15° shoulder to compensate for angulation^{97,128}. This implant was aimed at offsetting the extension of the sinus being installed along the anterior sinus wall. In addition to the 15° implant shoulder, abutments with a 5° to 8° angulation were proposed to further compensate, for up to 23°, the inclination of the implants in the bone¹²⁹. Afterwards, a list of specific angulated implants were reported to overcome the maxillary sinus pneumatisation¹³⁰(Figure 3).

Figure 3. I.T.I Bonefit 15-degree angled implant with a 5° (A) and 8° (B) abutment¹³⁰.

Kallus et al. described the angulation of an implant as a mesio-distal inclination largely parallel to the anterior wall of the sinus. A pilot case series was conducted to test the possibility of using angulated abutments with angles of between 15°- 30° to compensate the inclination of the implants mainly for '*aesthetic, functional and facilitative reasons*'¹³¹.

The technique of positioning angulated implants to avoid bone augmentation, especially sinus lift procedures, was described by Mattsson et al.¹³², who treated 15 patients with severe resorbed

edentulous maxilla; the maxilla could receive four or six additional implants. According to the technique described by the authors, the posterior implants were inserted tangentially to the anteromedial wall of the sinus. However, no additional information about the most appropriate angulation was provided.

Krekmanov et al.¹³³ were the first authors to report an inclination of approximately 30°-35° and 25°-35° for the tilted implants inserted in the posterior maxilla and the posterior mandible, respectively. If the angulation exceeded 30° of divergence, angulated abutments were used.

The above-mentioned technique showed very good implant stability, engaging the dense bone of the anterior sinus wall and the cortical bone of the nasal cavity with the use of long fixtures.

Tilted implants were not only used for edentulous patients. Aparicio et al.¹³⁴ reported, in a retrospective study, on 25 patients treated with 29 maxillary FPDs supported by 101 Brånemark implants out of which 42 were inserted tilted. After 5 years of follow-up, no significant difference in the marginal bone level (MBL) changes was observed between axial and non-axial positioned implants. The authors stated that an implant that diverged from its perpendicular trajectory to the occlusal plane over 15° was considered as angulated.

Another 5-year retrospective study involving 38 patients who received 43 FPDs supported by 111 AstraTech implants (Dentsply Sirona Implants, Mölndal, Sweden) reported no difference in bone loss between implants with an axial or non-axial position. The authors reported a mean angulation of the non-axial position implant of 17° (11-30)¹³⁵.

In 2003 Malo et al.¹³⁶ proposed the ‘all-on-4’ concept for the treatment of edentulous mandibles where the 2 posterior implants were inclined, according to a prefabricated guide, approximately 30° mesial to the mental foramina. The inclination of the implant was, thereby, corrected by an angulated abutment (30° or 17°) to get the screw access hole in the occlusal or lingual aspect. Consequently, the same researchers applied the concept to the edentulous maxilla¹³⁷.

IMPLANT ABUTMENT CONNECTION

Implants should be designed as a ‘one-piece’ single or a ‘two-piece’ component¹²⁸. The matching area between the two-piece implant is known as the implant abutment connection (IAC). The IAC is obtained through the use of a screw that is tightened, at a precise preload, to keep the two components together: the abutment and the implant. The IAC tends to avoid any mechanical drawbacks limiting the possible formation of a gap.

The preload force is determined by several factors such as material, the diameter of the components, and friction coefficient between the abutment and the implant. The elongation of the screw and its elastic deformation has to stay below the yield limits during the patient’s loading cycles to secure the connection.

The implant external hexagon was the first reported IAC design. The original Brånemark implant IAC comprised a flat area with a hexagon of 0.7 mm height. However, its primary use was not envisaged as an anti-rotational element (as it is today), but it was conceptualised to be adapted to the implant driver during the surgical procedure and aimed at controlling the insertion torque.

With the increased use of dental implants in partial and single-unit applications, the limits of the original design purpose of the Brånemark IAC were highlighted, especially the prosthetic screw abutment loosening and the consequent framework retention^{13,138,139}.

Technically, the external hexagon should have a height of 1.2 mm to provide adequate anti-rotational stability^{140,141}.

For a single-tooth replacement, especially in the frontal region, and immediate implant placement in extraction sockets, to prevent the collapse of the alveolar bone and soft tissue, Schulte and Haimke developed the Tübingen implant. This system subsequently became the Frialit-2 implant system and was the first to be designed with an internal IAC system^{142,143}.

IMZ (IMZ cylinder implants, Friedrichsfeld AG, Mannheim, Germany) was another implant system¹⁴⁴ designed with an internal IAC and employed, when it was first used commercially, to stabilise bars for overdenture and subsequently used in single-tooth restoration¹⁴⁵.

These types of internal IAC geometry were named 'clearance-fit'. They were based on a flat-to-flat butt joint connection with an internal anti-rotational system (index) varying in design depending on the implant brand¹⁴⁶.

In 1988, Sutter et al.¹²⁸ reported a different IAC of the ITI® implant, with an internal conical connection (ICC) with a cone shape of 8°. Another significant characteristic was that the IAC area was approximately 3 mm above the bone surface.

The purpose of this different IAC design was chosen for many reasons for instance: (i) microgaps in the IAC are outside the tissue preventing potential peri-implant infection; (ii) the transmucosal collar shape avoids a second surgical procedure; (iii) the insertion of the abutment is simple since the IAC is visible and not obscured by the presence of blood or saliva; (iv) the supra-crestal tissue seal is established during the primary healing phase; (v) a favourable mechanical joint adaptation between the two parts as 'lever arm'¹²⁸.

Even though the conical connection, introduced by the ITI® system, highlighted the advantages above, the supra-crestal IAC of this implant system had aesthetic drawbacks. In 1990, a new ICC implant named AstraTech implant system was tested in animals and subsequently in humans^{147,148}. The ICC had a cone geometry of 11°. This system was, subsequently, mechanically tested in different set-ups and compared to the external hexagonal butt joint implants¹⁴⁹, to the ITI® implant system¹⁵⁰ and the one-piece or two-piece conical joint within the same AstraTech implant system¹⁵¹.

In 1985, a screwless Morse taper implant system was developed (Bicon Dental Implants, Boston, USA). It was different from the

two-piece implant systems, and fastened by a screw, as described previously¹⁵². It had a 1.5° locking tapered connection using the engineering principles of the interface method between a hub and a shaft frequently used in hip prostheses¹⁵³.

From here on, many implant systems have been developed and are now available on the market. These can be divided in two main categories: the external or internal IAC¹⁵⁴.

The internal IAC consists of three main categories: the clearance-fit flat-to-flat butt joint connection, the ICC, and the screwless Morse taper connection. However, it is possible to identify a fourth category or subcategory, which is a combination of the previous three, where the IAC has different designs with the mating, with or without anti-rotational features, or with different conical designs¹³⁹.

The ICC was reported to prevent microleakage and the abutment screw loosening, granting a better fit under loading^{155,156}.

Another significant characteristic of the IAC flat-to-flat design was the platform-switching concept, where the diameter of the abutment is smaller than the one in the implant¹⁵⁷.

The ICC implants and the Morse taper implants had a joint that had an in-set in the IAC. The platform switching geometry was reported to have better results of bone level maintenance compared to a matching IAC¹⁵⁸.

Despite the different geometry of the implants on the market, and the advantages claimed by each implant company, in a large population of 1159 patients who were treated with 2010 implants, no differences between the clinical outcomes of the internal or external IAC implants were observed¹⁵⁹.

IMPLANT-PROSTHESES RETENTION TYPE

The retention between prostheses and implants, as reported in several scientific publications, is facilitated by a screw or cement.

The implant-prostheses retention was, as reported by the original protocol², screw-based before a cemented retention was introduced, especially for single-unit restorations. However, two main problems emerged with the screw-retained setup: loss of retention and impaired aesthetics due to the presence of the screw access holes^{138,140}. Different techniques were proposed to solve these issues^{142,143,160} and, with the introduction of new and different components on the market, cemented restorations began to be widely used¹³⁹.

The cemented retention was considered simpler than the screwed counterparts, giving a better passivity, improving aesthetics and facilitating the occlusion¹⁶¹⁻¹⁶⁴. The laboratory technicians could easily choose the abutment that was most appropriate for the given implant angulations, presence of space between arches and/or neighbouring pilasters¹⁶⁵. However, cemented restorations had some disadvantages, as in the case of severe implant lingual position leading to an over-dimension of the prosthetic restorations that may impinge on the tongue area.

Another important weakness of the cement retention was that cement remnants were claimed to trigger soft tissue inflammation and were suspected to be causes of peri-implantitis^{18,166-172}. In a systematic review, cement excess was present in 33% to 100% of the cases of peri-implantitis¹⁷³. Even though the authors stated that these cases might not be accurately used for prevalence data, excess of cement

was indicated as a possible risk factor for peri-implantitis. Moreover, it was argued that positioning the restorative margin in order to facilitate the cement removal was a crucial preventive factor for peri-implant diseases^{173,174}.

Even if no differences in terms of survival rates and MBL change were reported, it has been stated that cement retention could lead to more biological complications, while the screw retention was more associated with technical complications. It seems that the retrievability of the screw-retained restorations is preferable in controlling and maintaining the implant, and the soft tissue stability¹⁷⁵⁻¹⁷⁸. In the last 5 years, the emerging use of modified bridge screws to compensate for implant angulations has simplified the screw retention setup. This option allowed the screw access hole to be placed in positions that were more convenient for aesthetic correctness and occlusion¹⁷⁹.

A decision tree for selecting the most appropriate of the two retention setups for each case was proposed, and the authors¹⁸⁰ made the following suggestion:

‘screw retention may be recommended: i) in the presence of minimal interarch space (minimum 4 mm); ii) for FDPs with a cantilever design; iii) for long-span FDPs; iv) to avoid an additional risk factor with the use of cement and a possible cement remnant; v) in the aesthetic zone, for provisionalization of implants to enable soft tissue conditioning and finalization of the emergence and mucosal profile; vi) when retrievability is desired.

Cement retention may be recommended: i) for short-span prostheses with margins at or above the mucosa level; ii) to compensate for improperly inclined implants; iii) for cases where an easier control of occlusion without an access hole is desired for example, with narrow-diameter crowns’.

Additional types of retention were proposed to overcome the disadvantages of the above-reported connection types. They are the telescopic prostheses concept^{181,182} and the system with the horizontal screw retention at the lingual/palatal surface¹⁸³.

Another type of retention, based on friction resistance between the abutment, designed with cone geometry, and a prefabricated telescopic couple named ‘conometric retention’, was introduced and used in the beginning for removable prostheses in edentulous patients¹⁸⁴⁻¹⁸⁶. In the last few years, this type of retention, described

and reported by two different groups of clinicians in Italy, was changed from removable to a fixed one, aiming to eliminate the problem of holes in the screw-retained restorations and concerns of cement remnants in the cement restorations for FCDs and FPDs¹⁸⁷⁻¹⁹². Since 2019, this type of retention has been under investigation for use in single-unit restorations^{193,194}.

SCREW-RETAINED FRAMEWORK CONNECTION

Screw-retained multi-unit restorations, in contrast with cement retention systems, have been associated with a lower incidence of biological complications and easier retrievability. It has been associated with increased technical complications on the other hand¹⁷⁵.

According to the original protocol², the interposition of an abutment between the implant and the framework was always used albeit its precise biomechanical behaviour was not described in detail. The screw-retained abutment installation was considered a surgical procedure, and in 1985, Cox and Zarb¹⁹⁵ referred to the abutments as '*osseointegrated abutments*'. Guidelines were solely used to guide abutment selection according to the thicknesses of the peri-implant mucosa during the surgical procedure¹⁹⁶.

However, until that period, screw-retained abutments were available on the market with a restricted minimum height of 3 mm. This limited the implant-supported restorations in specific cases such as inadequate space between arches or the demand for highly aesthetic designs. In 1988, Lewis et al.¹⁹⁷ highlighted the possibility of avoiding the use of a screw-retained abutment with the introduction of the UCLA element. These types of plastic abutments were inserted in the wax design framework and cast together, resulting in final screw-retained implant level reconstruction.

With the UCLA abutment, three major advantages were reported: (i) possible implant-supported restorations in cases of inadequate vertical spaces, especially in posterior segments; (ii) aesthetically

improved, developing an ideal contour of ceramic around soft tissue; (iii) costs were reduced²⁹.

Regardless of the above reported clinical advantages, no statements were included on the biomechanical properties of an abutment level (AL) connection or the limitation of an implant level (IL) setup.

Hellden & Derand¹⁹⁸ were the first authors to inquire about the basis of the screw-retained abutments as ‘*shock-absorbing*’ components with specific reference to compensating for potential misfit between the framework and the implant. The authors described, in an *in vitro* study, an alternative to the conventional cast framework technique where laser technology was used to weld prefabricated titanium cylinders to a cast Ti-framework. This procedure aimed at reducing misfit and unpredictable stress to the peri-implant bone tissue or the components of the implant. Using this system, the authors reported very few mechanical complications in a 5-year prospective multicentre study in which FCDs and FPDs were directly screwed to internally connected implants¹⁹⁹. However, further clinical studies reported different outcomes using different implant systems. A retrospective 5-year clinical trial reported more technical and biological complications in the IL than the AL group²⁰⁰.

Takeshita et al. reported implant fractures when multi-unit Au-alloy-casted frameworks were screwed at IL²⁰¹. The authors reported that the laboratory procedure, during the casting steps, may have induced unpair stresses at the connection interface with possible risks of implant fracture. Additionally, a finite element analysis (FEA) study that simulated a bridge design, supported by two ICC implants with AL or IL connections with different misfits, revealed an increase in stress around the neck of the implant and misfit conditions in the IL connection. The authors suggested an AL setup as a preferable retentive option for implant-supported bridges²⁰².

Conversely, in a 2-year follow-up on the prosthetic maintenance of edentulous patients in the maxilla, treated with an IOD or an FCD, there were no complications when frameworks were IL connected at a trilobed internal connection implant (ReplaceSelect™, Nobel Biocare Services AG, Zürich-Flughafen, Switzerland)²⁰³.

Another publication reported data on the 91 FPDs with an IL screw retained connection supported by 229 implants. After a 5-year follow-up, the Zi frameworks had a cumulative survival rate of

90.5% and the authors reported no complications in the flat-to-flat implant-suprastructure connection, suggesting that this procedure is viable when a precise milling technique is used²⁰⁴.

MBL change was evaluated when 2 or 4 Straumann® Tissue Level implants (Straumann Holding AG, Basel, Switzerland) were splinted together for an IOD in service for 2 to 11 years. The implants placed in the maxilla reported more bone loss (1.145 ± 0.09 mm) than the implants in the mandible (0.81 ± 0.04 mm)²⁰⁵.

Another study followed 20 patients who were subsequently treated and rehabilitated with a screw-retained implant with an immediately loaded FCD in the maxilla with AstraTech implants. The MBL was located at 0.35 ± 0.29 mm from the implant-abutment connection after 18 months from the loading²⁰⁶.

In a 1-year randomised clinical trial, comparing AL and IL setups using fixtures with an external hexagonal connection (Nobel Biocare Services AG, Zürich-Flughafen, Switzerland), greater bone loss on IL restorations compared with an AL setup was observed²⁰⁷.

In another clinical trial, the 2 central implants (NobelActive, Nobel Biocare, Zürich-Flughafen, Switzerland), in a 4-implant immediate mandible rehabilitation, were allocated randomly to an IL or AL group. No difference between MBL changes of the groups after 5 years was observed and the authors concluded that the use of the abutment may not be necessary²⁰⁸.

To the best knowledge of the author of the present thesis, in absence of precise data and clinical recommendations, the use of an IL set-up, as a feasible solution, remains debatable²⁰⁹.

FRAMEWORK DESIGN

In the beginning of the osseointegration, the framework used was cast with Au-alloy material and the lingual and the pontic faces of the bulk were entirely finalised with metal with the vestibular and occlusal sides in resin. If a metal-ceramic framework was the preferred option, only the facial aspect was settled with veneering material while the occlusal, lingual and the pontic area remained in metal². Additional descriptions were reported by Lundqvist & Carlsson in 1983²¹⁰ and Loos in 1986²¹¹. The framework comprised Au-alloy metal in all the pontic surfaces throughout the occlusal level in the posterior segments and the cingulum level in the anterior region.

From this original description, immediate changes were proposed because of three main reasons: (i) the great amount of gold used with the associated costs; (ii) the related bio-technical complications due to the heavy bulk of the material that transferred unpaired strain and stress to implant components and bone; (iii) to guarantee a sufficient strength in the connection between the distal implant and the cantilever posterior segment.

Framework Material

In 1985, Cox and Zarb¹⁹⁵ reported on less expensive methods using silver-palladium alloys. Regardless of the alloys used, the suprastructures had to follow precise parameters: *‘(i) it must not interfere with desired cosmetic/aesthetic design; (ii) it must accurately and passively fit the osseointegrated abutments; (iii) it must have sufficient load-bearing capacity to stand up to both functional and parafunctional activities; (iv) it should be made of materials that are*

corrosion resistant; (v) it should be reasonable in cost and preferably quite easy to fabricate'.

To overcome the biomechanical sequela due to the heavy bulk of the material that transferred unpaired strain and stress to implant components and bone, the use of the veneering material in the occlusal aspect with a reduced framework design even in the lingual sides was suggested⁵⁷. The occlusal layer area had the property to absorb the forces, at a certain velocity, resulting in lower pick value and protecting the implant-abutment and the implant-bone interfaces²¹².

However, even if this modification resulted in a less heavy structure with more resin, functioning as a shock-absorbent system, veneering fractures started to appear more frequently due to lower bearing capacity of the entire reconstruction^{13,14,57,213}.

Cantilever

The cantilever was reported at the initial phase of the implant-supported prostheses reconstruction era to be restricted in dimension²¹⁰ or with a maximum extension of 12 mm on each side of the mandible²¹¹.

The cantilever was subjected to deflection under the loading condition summarised in the Euler-Bernoulli's equation applied to an 'end-loaded cantilever beam': ' $D = (F \times L^3 \times \text{constant}) / (E \times W \times H^3)$ ' where F is the force acting on the tip of the cantilever, L is the length, E is the modulus of elasticity of the material, and W and H are the width and height of the cantilever, respectively. If the span doubles, the deflection increases eight-fold²¹⁴.

Further alternative prosthodontic design techniques for the fabrication of implant-supported frameworks in edentulous patients in the mandible were described. They included the design of a 20 mm and a 15 mm cantilever in the lower and upper jaw, respectively. The shape used was in accordance with mechanical engineering proprieties of the 'I-beam'. This concept reduced the bulk and weight without loosening the stiffness and strength of the framework²¹⁵.

To understand the strength in different framework designs, with reduced suprastructures and the possible complications of the cantilevers, Staab and Stewart²¹³ reported a theoretical analysis of the four beam patterns, with a 20 mm cantilever: the L-shaped beam²¹⁶,

the I-shaped beam¹⁹⁵, the U-shaped beam and the elliptical-shaped configuration.

The authors concluded that no differences were present in the above-mentioned configurations. Theoretical calculation tried to predict the length of the cantilevers based on the anterior and posterior position of the implants²¹⁷⁻²¹⁹. However, analytical tests are limited to simulating a clinical situation where different anatomical characteristics represent the main challenge. Other authors reported their own experiences on different framework designs intended to enhance the robustness of the connection portion between the cantilever and the distal abutment^{220,221}.

Framework Manufacturing

After the experience of Zarb and Jansson in 1985²²², in using different alloys like the silver palladium alloys as an alternative to Au-alloys²²³⁻²²⁵, Jemt reported a different technique for the production of frameworks using prefabricated Ti components welded to Ti bars in 1992²²⁶. The Ti material and components allowed increased biocompatibility and low weight compared to Au-alloys frameworks²²⁵.

Subsequently, different laser welding techniques were employed in melting the cast Ti bars to prefabricated Ti abutments²⁰⁰. However, some fractures were reported in the laser welding cast Ti procedures²²⁷ and its use was finally dismissed and substituted by the CAD-CAM milled technique as a better alternative to control distortions²²⁸ and enhance strength during service³⁰. Moreover, with the CAD-CAM system, the size of frameworks could be additionally reduced compared to the Au-alloy^{229,230}.

Ti, began to be regarded as the most suitable material with clinical results comparable to the cast Au-alloy framework^{9,10,231}.

According to the technique described by Jemt³⁰, the framework was designed in acrylic, by the technician and, thereafter, scanned and milled from a solid block of Ti. Thanks to the digital evolution, more precise laboratory scanners were produced. Moreover, various highly sophisticated milling machines have been developed for each specific material²³². The precision in the production accuracy was set at $<10\mu\text{m}$ ^{233,234}. Frameworks can be milled in different materials; most commonly Ti, Zr and Co-Cr. Titanium has been reported to have a higher long-term success rate and offer a better fit in multi-unit

frameworks, from its introduction in the late 1990s, in comparison to Zr^{10,235,236}, while the latter, being metal-free, is mainly used to enhance aesthetics. Co-Cr presents the same excellent mechanical properties and performance as Ti; however, it can be more versatile in the laboratories, especially when ceramic is chosen in the veneering process²³³.

In the last few years, the subtractive manufacturing (SM) technique, typical of the milled process, matched the use of an additive manufacturing (AM) production²³⁷. With the SM technique, the framework shape design and the bar size are limited due to the reduced geometrical flexibility in the machine axis. On the contrary, with the use of AM procedures, suprastructures can be designed in unlimited geometries.

The AM was defined by the ASTM F42 Technical Committee *the 'process of joining materials to make objects from three-dimensional (3D) model data, usually layer upon layer, as opposed to SM methodologies'*²³⁸.

Among the different methods in the AM procedures, three are mainly used in dentistry: the selective laser melting, the selective laser sintering (SLS) and the electron beam melting using an electron beam instead of a laser^{239,240}.

With this new technology the quality control of the production is potentially improved and better results are guaranteed compared to the conventional standard methods.

Fit

When two components are assembled, the clearance between the two mating parts is defined in engineering terms as 'fit'. The fit between parts, generally described as 'shaft and hole', defines a relative position of the sections.

Since the friction of the interface fit, which fastens the two parts, generates tensile and compressive forces, tolerance is introduced as a permissible limit in variations between the maximum and minimum size of the components. Accurate dimensional tolerance is a consistent part of the micromechanical production and affects the function of the assembled part as a direct consequence of fabrication costs²⁴¹.

Patterson²⁴² defined the fit in implant dentistry in four different levels as follows:

‘Perfect Fit: all mating surfaces are in contact and aligned without the application of any external forces.

-Passive Fit: somewhat less than perfect, but the application of any external force to produce a perfect fit has a negligible effect on the performance of the prostheses.

-Active Fit: external forces, when applied, can produce a perfect fit, but the forces are detrimental to performance of the prostheses.

-Poor Fit: external forces cannot produce a perfect fit.’

The accuracy of fit was described by Cox and Zarb in 1985¹⁹⁵ in the framework casting procedures. The authors evaluated three different alloys for the fabrication of the suprastructure: Au alloy, silver palladium alloy and Co-Cr alloy. The average misfit between the framework and the abutments was 39 μm , 29.3 μm and 18.8 μm for Au alloy, silver palladium alloy, and Co-Cr alloy, respectively.

The fit level depends on two main aspects: firstly, the quality control in the production of the prefabricated implant components and, secondly, the dental laboratory framework constructions.

Additionally, up to a certain calculated tolerance, there is an increased discrepancy between the parts due to the mechanical process. The ideal (nominal value) geometrical design of a component is, in reality, manufactured (actual value) with an accepted approximation of imperfections as a consequence of the quality control procedure²⁴³. Moreover, implant companies may decide to use suppliers, in the components production chain, for a variety of reasons such as accelerating delivery, stronger quality control or reducing operating costs. Outsourcing manufacturing is a common approach but could have some challenges. Suppliers, although they strive to have the same accuracy in the production phase as the established implant companies, are obliged to set their threshold depending on their facilities. As a result of this industrial process, components may have differing levels of tolerance, introducing potential misfit in the final rehabilitation^{138,244}.

The process that involves impression, models, wax, casting, and finalisation of the framework counts numerous steps. Each clinical and laboratory passage includes a potential error that ends up in an overall misfit at the final implant-supported prosthetic delivery^{162,245}.

The sum of these two above-reported factors (known tolerance and the laboratory processing) leads to a total misfit critical to the success or failure of the reconstruction.

A misfit between implant and framework may introduce uncontrolled strain and stresses asserted as a possible cause of technical and biological complications¹⁶² such as screw/abutment loosening or fractures, framework fracture and in the worst-case scenario, implant fracture and implant loss²⁴⁶.

However, as reported in a systematic review by Abduo and Judge, the negative biomechanical sequelae related to the presence of a misfit are not scientifically supported and the only complication related to a presence of an unfitting implant framework connection, is screw loosening. Reported complications as the fracture/chipping of the veneering suprastructure and the biological ones, may not be completely attributable to a misfit. Moreover, a potential implant displacement with bone remodelling may compensate for the magnitude of strain at the bone to implant interface²⁴⁷.

From a clinical prospective, a classification, according to varying levels of the detached gap, was proposed. The values of gaps that exceed the 100 μm were not considered clinically acceptable. However, the clinical evidence was insufficient and the potential gap, in screw-retained multi-unit reconstructions, was not found to affect the MBL change during service. The interfaces and components, that comprise the implant-framework restorations complex, were considered to be able to compensate for the uneven strain²⁴⁸.

This statement was confirmed by a clinical trial in which patients edentulous in the maxilla were rehabilitated with a fixed or removable full arch reconstruction, with a maximum range of gap of 275 μm . This study did not show any correlation between bone loss and misfit, indicating that a certain grade of compensation occurs clinically²⁸. Another randomised control trial (RCT) compared of 20 partial segments with fit or misfit restorations. A perfect fit was never achieved, even in the fit group. The values ranged from 1.06 μm to 135.59 μm in the fit group and 40.80 μm to 533.08 μm in the misfit group. The authors concluded that a certain misfit is biologically acceptable and tolerated by the body²⁴⁹.

However, a clear definition of what is an acceptable level of misfit does not exist²⁴⁷. Additionally, all superstructures have a potential

misfit, which are clinically tolerated, clinicians and technicians should aim to achieve the best passive fit possible to reduce potential risk complications²⁵⁰.

Mechanical loading test

Fatigue theories

Fatigue is a physical phenomenon that characterises all materials under a prolonged loading condition, weakening their efficiency. The loading condition can be divided into static and dynamic.

The static model is typically used to test the fracture strength of a component or a joint and typically follows the ISO standard test. However, the masticatory function imposes a repetitive loading on the implant-prostheses biomechanical-interfaces and components that cannot be described with static loading theories.

For this reason, cycling loading models are considered more clinically relevant than static ones. The main differences between the two tests (static and failure) are the failure modes. Static theories are well understood and examine the limit, ultimate tensile strength (UTS), of the material and the failures that occur when a continuous constant force is applied.

Fatigue theories intend to analyse failures that occur to a material/component/joint under a repetitive applied force below the yield limit. Fatigue phenomena are very complex to predict and are both sudden and catastrophic. They depend on the type of loading (axial, bending, torsion, combined), on thermal conditions, on material compositions and production (voids, inclusion, imperfection, flaw). Typically, the fatigue failure is characterised by a crack propagation which has three stages: (i) crack nucleation (inclusion, localised yielding, slip along margins), (ii) crack propagation (consecutive progress), and (iii) unstable crack (material cannot maintain additional stress, quick fracture).

The stresses in fatigue failure models are typically presented in three different repetitive load scenarios: (i) the fully reversed, (ii) the fluctuating, and (iii) the combined loading.

The fully reversed is typically reported in the S-N diagram where S is the applied stress and N is the number of cycles. The failure theories were developed during the industrial revolution to analyse the fatigue of metals used in railway vehicles (locomotive, driving

wheels, boilers, firebox components) that failed under loading and pressure. The S-N curve relationship was described by Wöhler in 1867²⁵¹ and represents the fatigue life of a material that bends equally, meaning tension and compression in a fully reversed stress at a specific load for several cycles. This curve represents the endurance or fatigue limit below which a specimen could be subjected to specific stress for an infinite time scenario. It is reported, according to the S-N theory, that the material of investigation does not present any failures before 1×10^6 cycles to be considered safe and be described as having an infinite life. In the aerospace industry, the limit is fixed at 1×10^9 to ensure the safest conditions possible. The S-N diagram is divided into three aspects: low fatigue, medium fatigue, and high fatigue with the cycles between 1×10^2 to 1×10^3 , 1×10^3 to 1×10^6 , and 1×10^6 to 1×10^9 , respectively.

The fluctuating theories represent a stress concentration in which the midrange stress is not equal to zero, as in fully reversed stress, implying that tension and compression are not equally bended. It is calculated according to the formula of the mean stress level (σ_m) defined as $\sigma_m (\sigma_{max} + \sigma_{min})/2$. Fluctuating theories are based on Goodman, Soderberg, and Gerber curves. The approaches differ in the ability to estimate or underestimate a potential failure²⁵².

The combined loading theories are applied when more than one stress is present at the same time. These forces, much closer to a real scenario, subject the investigated component to axial flexion and torsion stresses at the same time and different frequencies. The mathematical models of the combined theories are aimed at analysing each category of stress separately and together, calculating the interaction with equations and sub-equations according to the S-N curve or fluctuating theories reported above²⁵³.

The theories used to understand the behaviour and the capacity of certain specimens represent a pure analytic analysis that requires confirmation with prototypes tested *in vitro* and *in vivo* experimental research.

Finite Element Analysis

The FEA is a simulation, used in engineering, to calculate the distribution of the stress and strain on any physical object.

The FEA provides an approximate solution and tries to satisfy the equilibrium equation that has to be zero ($\pi:f.int -f.ext =0$), where $f.int$ represents internal forces and $f.ext$ represent external forces, which implies that the total potential energy of a system, in a static condition, does not vary when stresses are imposed on each point of a certain object. If a potential displacement leads to an unstable condition, a deformation is produced in the system²⁵⁴. This principle was the basis of the Rayleigh-Ritz method which tried to give approximate solutions to a complicated system that did not satisfy the equilibrium non-zero condition of the minimum potential energy and was the origin of the FEA^{255,256}.

The FEA was developed independently from engineering by the aerospace industries or mechanical companies. They aimed to optimise the mechanisms of each component in the design phase limiting the production of prototypes and experiments. The FEA divided the system of interest into many small different elements or subregions, finite in numbers, each of which keeps the proprieties of the pristine material.

The number of elements is analysed through an approximation obtained by mathematical equations used to quantify the physical interaction at a given condition of load. The elements are connected with nodes and a virtual system is built and processed with a computational model to estimate a certain behaviour²⁵⁷.

In 1973 Tesk and Widera²⁵⁸ applied the Rayleigh-Ritz method with the FEA to an implant system and concluded that, due to the different possibilities and combinations of materials, a large investigation had to be performed. As computational systems and software was evolving other authors started working on the use of the FEA in implantology²⁵⁹⁻²⁶¹. The load transferred for an implant rehabilitation to the surrounding bone depends on the type of (i) load, (ii) prosthetic reconstruction, (iii) implant-abutment-framework connection, (iv) implant, and (v) the quality and quantity of recipient bone²⁶². Different kinds of analyses have been performed in the last few decades mainly because it is difficult to replicate the complexity of the masticatory system of a human being in a model. Researchers are putting their efforts into achieving validated models with a high level of reliability to better understand the implant biomechanics²⁶³.

COMPLICATIONS IN IMPLANT-SUPPORTED PROSTHESES

Medical devices, albeit benefiting patients, can have and create complications. Complications may arise due to factors such as fatigue failure caused by wearing, imperfections, inclusions, or flaws in production²⁵³. Biomaterial associated infection²⁶⁴, may also cause complications. It is defined as an immunological reaction to a micro-organism that can adhere to a foreign body or material and promote the formation of a biofilm.

Regardless of the above-reported phenomena, complications can negatively impact the survival and/or success of any medical intervention and they need to be carefully considered by professionals.

Success, survival, and failure

Success, survival, and failure refer to the absence or presence of complications that affect the implant-prostheses reconstruction during a period of investigation.

Semantically, (i) success, represents a condition free of any complications as it was at the moment of the final delivery, (ii) survival, describes a state where the reconstruction stays in function regardless of complication, and (iii) failure is the loss of the entire implant-supported restoration or the prostheses reconstruction^{26,265}.

Success, survival, and failure are defined by thresholds and sub-thresholds, and could be misclassified by the examiner^{26,266,267}.

This could lead to an under- or overestimate of the real clinical picture of total complication rates and, consequently, data has to be

interpreted with caution^{12,171}. Thus, the scientific community requires detailed reporting on the complications in clinical trials³¹.

Technical complications have more distinguishable threshold levels since a fracture that involves a screw, an abutment, a framework or suprastructure part is simple to categorise in dichotomous variables. In contrast, the definition of implant success has been discussed since 1986 with the Albrektsson's criteria.

The implant success criteria were defined in 1979 by Schnitman et al. and subsequently a revisited criterion was published by Albrektsson and co-authors^{22,268} as shown in Figure 4.

<p><u>NIH-Proposal, Schnitzen and Shulman, 1979</u></p> <ol style="list-style-type: none"> 1. Mobility of less than 1mm in any direction. 2. Radiologically observed radiolucency graded but no success criterion defined. 3. Bone loss no greater than a third of the vertical height of the implant. 4. Gingival inflammation amenable to treatment. Absence of symptoms and infection, absence of damage teeth, absence of paresthesia and anesthesia or violation of the mandibular canal, maxillary sinus, or floor of the nasal passage. 5. To be considered successful, the dental implant should provide functional service for five years in 75% of the cases. 	<p><u>Proposal by Albrektsson, Zarb, Worthington and Eriksson, 1986</u></p> <ol style="list-style-type: none"> 1. That an individual, unattached implant is immobile when tested clinically. 2. That a radiograph does not demonstrate any evidence of peri-implant radiolucency. 3. That vertical bone loss be less than 0.2 mm annually following the implant's first year of service. 4. That individual implant performance be characterized by an absence of persistent and/or irreversible signs and symptoms such as pain, infections, neuropathies, paresthesia, or violation of the mandibular canal. 5. That, in the context of the above, a successful rate of 85% at the end of a five-year observation period and 80% at the end of a ten-year period be a minimum criterion for success.
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Figure 4. Criteria for implant success²².

In a prospective 10-year study on the ITI® dental implants²⁶⁹ the following criteria for defining the survival and success rates were applied: (i) absence of mobility, (ii) absence of persistent subjective complaints (pain, foreign body sensation and/or dysesthesia), (iii) no probing pocket depth (PPD) > 5 mm, (iv) no PPD = 5 mm and bleeding on probing (BoP)+, (v) absence of a continuous radiolucency around the implant, and (vi) annual vertical bone loss < 0.2 mm (mesially or distally) after the first year of service. The authors used the parameters set out by different previously published success criteria^{22,270-272}. Interestingly, the authors stated that, depending on the threshold applied, success rates varied greatly when comparing different studies²⁶⁹.

In 2007, during the ICOI Pisa Consensus Conference²⁷³, categories for success, survival, and failure implants were reported, as indicated in Table 1.

Table 1: Health Scale for Dental Implants (Consensus ICOI 2007)²⁷³

Implant Quality Scale	Clinical Conditions
I) Success (optimum health)	a) No pain or tenderness upon function b) 0 mobility c) <2 mm radiographic bone loss from initial surgery d) No exudates history
II) Satisfactory survival	a) No pain or tenderness upon function b) 0 mobility c) 2-4 mm radiographic bone loss from initial surgery d) No exudates history
III) Compromised survival	a) May have sensitivity on function b) 0 mobility c) Radiographic bone loss 4 mm (less than 1/2 of implant body) d) Probing depth 7 mm e) May have exudates history
IV) Failure (clinical or absolute failure)	a) Pain on function b) Mobility c) Radiographic bone loss > 1/2 length of implant d) Uncontrolled exudate e) No longer in mouth

Ong et al.²⁷⁴, addressed the importance of standardising the descriptions of implant outcomes and thereby making a comparison between clinical trials possible. They suggested that the criteria for defining the success of an implant had to consider the definitions proposed by Albrektsson and Isidor²⁷⁵ as well as the ones indicated by Karoussis et al.²⁷⁶ and Roos-Jansåker et al.²⁷⁷. These criteria were an incidence of PPD ≥ 5 mm with BoP/suppuration and radiographic bone loss ≥ 2.5 mm or bone loss extending ≥ 3 threads at a follow-up of at least 10 years.

In 2012, in a systematic review on the success criteria in implant dentistry, it was reported that the criterion of a bone loss of 0.2 mm after the first year, as defined by Albrektsson in 1986, should be questioned because there are different implant designs and characterisations of contemporary implantology. Moreover, a successful outcome should cover the entire implant/prostheses complex and the patient's expectations. The authors reported four parameters for evaluating implant success (i) MBL change, (ii) peri-implant soft tissue, (iii) prostheses, and (iv) patient subjective evaluations. The authors stated that success rates decreased with increasing criteria¹⁵.

In a recent consensus on peri-implant conditions, specific thresholds were recommended for assessing the normal peri-implant condition, mucositis, and peri-implantitis. The latter condition was defined as (i) the presence of bleeding and/or suppuration on gentle probing, (ii) increased probing depth compared to previous examinations, and (iii) the presence of bone loss beyond crestal bone level changes resulting from initial bone remodelling. Additionally, in the absence of previous examination, the authors stated that peri-implantitis can be based on (i) the combination of the presence of bleeding and/or suppuration on gentle probing, (ii) probing depths of ≥ 6 mm, and (iii) bone levels ≥ 3 mm apical of the most coronal portion of the intraosseous part of the implant²⁷⁸.

Risk factors for complications

Risk factors are conditions that increase the probability of a disease. However, the threshold of a behaviour that can be causally related to a precise outcome is still uncertain^{279,280} and a combination of factors may cause complications¹⁸.

Risk factors for technical complications

Several factors that increase the risk of technical complications have been reported.

Salvi and Bragger²⁸¹ reported that these are most associated with complications: (i) the absence of a metal framework in overdentures; (ii) the presence of cantilevers > 15 mm with bruxism; (iii) the length of reconstruction; (iv) a history of repeated complications.

With regards to the extent of the reconstruction, Karlsson et al.²⁸² also noted that this aspect was strongly associated with complications as a risk indicator. Furthermore, the authors reported that screw retained short bridges had a higher risk of losing retention in comparison to longer ones and even compared to cement retention. Similarly, to what was reported by Salvi and Bragger, the length of the cantilever was associated with a higher risk of screw loosening and chipping compared to the ones without cantilever.

Males had a higher risk than females²⁸² when it came to the fracturing of the veneering material. This is one of the most commonly reported complications. Moreover, having an opposing removable dentition, such as a denture, instead of a fixed dentition, increased the

risk of fracture. Other authors have reported a higher risk of chipping and fracture in the maxilla than in the lower jaw^{56,283-285}.

Further, it was reported that the risks of some complications were related to the types of fixtures used²⁸². This was already highlighted by Brägger¹⁷ who reported that complications are '*system-specific*'. A retrospective study based on 2,670 patients confirming the relation between type of implant and complication. The authors reported that the grade of titanium and the implant diameter and length are risk factors for implant fractures. The same authors indicated, as further risk factors for implant fracture, the presence of a cantilever and bruxism²⁸⁶.

Finally, a higher risk of attrition was reported when implant-supported rehabilitations were performed by general dentists compared to specialists²⁸².

Risk factors for biological complications

Heitz-Mayfield²⁸⁷ reported some risk factors associated with peri-implant diseases stratified by supporting evidence. Risk indicators for peri-implant disorders with substantial evidence were poor oral hygiene, history of periodontitis, and smoking habits. Limited evidence has reported diabetes and alcohol consumption as risk factors for peri-implantitis, and conflicting and limited evidence have indicated genetic traits and implant surface as risk factors.

It was further reported that moderate or severe peri-implantitis was displayed in patients with a history of periodontitis. Moreover, patients with smoking habits had a higher risk of losing an implant in the early period²⁸⁸⁻²⁹⁰.

In 2015, the summary of a consensus conference reported that peri-implantitis has a complex aetiology, and potential risk factors were (i) inadequate oral hygiene, (ii) microbial biofilm composition, (iii) excess of cement, (iv) a history of periodontitis, (v) genetic factors, smoking, (vi) inadequate maintenance, and (vii) systematic disease¹⁶⁹. The excess of cement, mis-fitting prostheses, and history of periodontitis were pointed out as possible risk factors for peri-implantitis in a large US cohort of 2127 patients who were treated with 6129 implants¹⁷¹. Prosthetic design, especially related to the large crown contour, with limited accessibility for the self-care procedures,

was also reported as a risk factor for peri-implantitis²⁹¹, especially in patients with a history of periodontitis¹⁷³.

Further emphasis on the '*system-specific*'¹⁷ risk of complications, where a certain types of implants developed less peri-implantitis than others was also reported^{171,289}.

Apart from the role of smoking and history of periodontal disease, maintenance therapy was claimed to play a crucial role in preventing peri-implant disease^{174,292}.

Technical and biological complications

Berglundh et al.¹² defined two main categories of complications related to the implant-prostheses reconstructions: technical and biological.

Technical complications are mechanical damages of the implant-related components and the superstructure.

Biological complications were defined as inflammatory processes that refer to a '*disturbance*' in the healthy peri-implant hard and soft tissue status.

A complication was defined by the Glossary of Oral and Maxillofacial Implants as an 'unexpected deviation from the normal treatment outcome. It is generally classified as either technical or biological, e.g., surgical complication, haemorrhage, damage to the inferior alveolar nerve, infection, delayed wound healing, or lack of osseointegration'²⁹³.

Moreover, some authors suggested a different classification based on visits needed to manage the complications and the related costs of maintenance as follows^{282,294}:

(i) Minor complications, when the complication is managed chair-side in a one-off visit. These are said to occur when it has been possible for the chipping to be polished, or bridge-screw and/or abutment to be retightened or re-placed, if broken.

(ii) Major complications, when the complication needs different interventions for repairmen. A complication is considered major when a fracture of the prosthetic material has to be managed by the dental technician and subsequently at least two or more visits are requested.

(iii) Catastrophic complications, when a complete renewal of the protheses is required. It mainly happens for cases of severe wearing, framework fracture or implant fracture.

Technical complications

Technical complications affect implant-related components and the prosthetic suprastructure and include the following:

- chipping or fracture of the prosthetic material,
- bridge screw and/or abutment screw fracture or loosening, abutment fracture,
- fracture of the framework material, and
- implant fracture.

As reported in Tables 2 - 3, the complications of FPDs and FCDs vary with major reviews and meta-analyses; however, they all confirm that the most frequent complications are the chipping or fractures of prosthetic material.

Table 2. Complications rates in FPD in different systematic reviews and metanalyses.

	Berglundh et al. 2002 ¹²	Pietrusson et al. 2004 ²⁵	Pietrusson et al. 2012 ¹⁴	Heydecke et al. 2012 ⁸¹	Pietrusson et al. 2014 ³¹	Millen et al. 2015 ²⁶	Sailer et al. 2018 ²⁹⁷	Pietrusson 2018 ¹⁷⁸	Goodacre et al. 2018 ²⁹⁸
	5Y	5Y	5Y	5Y	Till 2000 After 2000 5Y	Cement Screw	Metal-ceramic 5Y	Internal connection 5Y	External connection 5Y
Total number of Technical complications									
Abutment fracture/failure									
Abutment or occlusal screw fracture		2.5% (1.6-4.7)	1.3% (0.7-2.3)	16.0%	2.2% (1.1-4.1)	0	15.1% (11.2-20.4)	9.4% (3.9-21.5)	12.2% (4.9-28.6)
Abutment or occlusal screw loosening (screw)		2.5% (1.6-4.7)	5.3% (3.6-7.7)	3.2%	5.2% (3.8-7.1)	0	0%	2.8% (1.1-6.7)	0.7% (0.1-6.9)
Abutment or occlusal screw loosening (cement)					4.0% (2.2-7.0)		0%	0.2% (0.06-0.8)	1.8% (0.5-6.0)
Framework Fracture	0.24%		0.5% (0.2-1.3)		1.0% (0.4-2.4)	0.29 [0.02-3.44]	4.1% (1.1-14.5)	0.9% (0.5-1.5)	2.0% (0.7-5.4)
Implant Fracture	0.74%	0.4% (0.1-1.2)	0.5% (0.2-1.1)		0.5% (0.2-1.5)	0	0.2% (0.06-0.7)	0.2% (0.06-0.7)	0.2% (0.02-1.2)
Veneers fracture or chipping		13.2% (8.3-20.6)	13.5% (8.5-20.8)	58.8%	19.2% (14.4-25.5)	0	11.6% (6.7%-19.7%)	6.7% (1.4-28.3)	5.1% (2.2-11.3)
Fracture of porcelain veneers								3.3% (1.2-8.6)	3.7% (1.3-10.3)
Loss of retention		2.9%	4.7% (2.6-8.5)			0.30 [0.02-4.16]		3.0% (1.3-6.6)	4.2% (1.3-13..1)
Failure of the reconstruction						0.94 [0.09-9.72]			
Ceramic chipping with repair									
Restoration lost due to ceramic fracture		8.6% (5.1-14.1)	8.5% (5.5-13.2)	20.2%- 53.0%			4.7% (0.9%-22.4%)	5.6% (2.5-10.7)	4.8% (1.6-13.6)
Total number of Biological complications									
Soft Tissue complication	0.15%								
Peri-implantitis	6.47%								
Bone Loss > 2.0mm	1.01%								
Peri-implant mucositis									
Implant loss during function	2.49%- 3.07%								
Significant marginal bone loss					7.4% (3.6-14.8)	0	3.1% (1.0%-9.2%)		
Soft tissue recession					9.4% (6.3-13.8)			5.6% (2.5-10.7)	0% (0-0.6)
Total Complications rate			33.3%		3.3% (1.3-8.6)	0	1% (0.3%-3.3%)		
Combined Complications					40.1% (39.9-41.5)	0			
					27.3% (19.8-36.9)				

Table 3. Complications rates in FCD in different systematic reviews and metaanalyses.

	Berglundh et al. 2002 ¹²	Bozini et al. 2011 ¹³ Metal acrylic			Heydecke et al. 2012 ⁸¹	Papaspirtidakos et al. 2012 ¹⁵ Metal acrylic		Pjetursson et al. 2014 ³¹ After 2000	Millen et al. 2015 ²⁶ Screw Complications rate x 100Y [95% CI]	Goodacre et al. 2018 ²⁸ > 1 year	Wong et al. 2019 ²⁹⁹ Metal ceramic All-ceramic		Bagegni et al. 2019 ³⁰⁰ Metal ceramic All-ceramic		
	5Y	5Y	10Y	15Y	5Y	5Y	10Y	5Y			5Y	5Y	6.77Y	5.3Y	3.6Y
Total number of technical complications								53.2%	19.44 (11.08-34.09)						
Loss of retention									1.13 (0.26-4.87)						
Abutment screw fracture		2.1%	4.3%	6.3 %				5.8% (1.5-20.9)	0.15 (0.05-0.52)	2%	0%	0%			
Bridge screw fracture		4.1%	8.0%	11.7%	16.0%	20.8%			0.52 (0.15-1.88)		0%	0%			
Abutment screw loosening		4.7%	9.2%	13.4 %	1.9%			9.0% (3.1-24.4)	0.74 (0.10-5.33)		0.91%	0%	7%	3%	4%
Bridge screw loosening		5.3%	10.3%	15.0%					1.75 (0.63-4.87)	1%	0.72%	1.43%			
Framework Fracture	0.54% (0.42-0.66)	3.0%	6.0%	8.8%		8.5%	16.9%		0.61 (0.19-1.99)	5%	0.43%	0%			
Framework Fracture Overdenture	1.90% (1.73-2.06)			4.2% 15.5%					0.15 (0.00-4.35)						
Implant Fracture	0.08%														
Implant Fracture Overdenture	0.38%														
Veneer fracture or chipping		30.6 %	51.9%	66.6 %	39.7%	33.3%	66.6%	25.3%(17.2-36.2)	10.04 (4.48-22.48)	28%	22.1%		22%	15%	8%
Fracture of porcelain veneer									8.95 (1.25-64.13)	12%					
Material wearing		17.3%	31.6%	43.5%		10.0%	20.0%			15%					
Aesthetic deficiency		3.1%	6.1%	9.0%		16.2%	32.4%			9%					
Total replacement of the veneering															
Total number of Biological complications					2.0% - 35.5%				7.61 (4.55-12.72)						
Soft tissue complications	0.19%								0.62 (0.06-6.97)						
Peri-implant mucositis									1.61 (0.56-4.62)						
Peri-implantitis									0						
Bone Loss > 2.0mm	0.71%														
Implant loss during function	3.78%								2.21 (0.63-6.71)	10%					
Hyper trophy or Hyperplasia of tissue	2.72% - 3.42%														
Inflammation under prosthesis						13.0%	26.0%								
						5.6%	11.3%								

Chipping or fracture of the prosthetic material

The most reported technical complication is the chipping/fracture of the prosthetic reconstruction (Tables 2 - 3).

A meta-analysis on the complications rates on FCD, reported that after 15 years of service, 70% of all the prostheses reported some forms of veneering fractures¹³. In another systematic review with up to 5 years of follow-up, it was reported that veneering fracture occurred in 39.7% and it was the most reported technical complication for FCDs⁸¹.

The same findings were reported in another systematic review on the biological and technical complications of FCD rehabilitation at 5 and 10 years. It was reported that the chipping or fracture of the veneering material had an incidence of 33.3% at 5 years and 66.6% at 10 years¹⁵.

This data was corroborated by Pjetursson et al.³¹, who reported that the incidence of fractures of the veneering material for FCD was 25.3% (17.2-36.2) in a mean observation period of at least 5 years.

Similar data were reported in a recent systematic review and meta-analysis and the incidence rates for chipping were between 8% and 22%, depending on the material used (ceramic or resin)³⁰⁰.

Moreover, chipping or fracture of the prosthetic material for FPD were inferior compared to FCD ones²⁹⁶. It should be noted that recent reviews have reported lower complication rates^{178,297,298}.

Screw loosening/fracture

Bridge screw loosening/fracture is mainly related to multifactorial phenomena, with misfit being the most important one^{247,248,301,302} (Tables 2 - 3).

Abutment and/or bridge screw loosening were reported to be frequent, especially, at the beginning of the osseointegration period in single or partial rehabilitations with up to 50% screw-loosening during the first year of loading^{114,303}.

Screw loosening had a tremendous reduction after 1991, following the development of new designs for the restoration components. As reported in a retrospective study on 1170 implants followed for more than 10 years, the abutment loosening decreased from 46% to 3.2%³⁰⁴. Another factor related to the reduction in screw loosening or fracture rates was the change of the IAC shape^{147,301,305}. It was

reported that a higher incidence was related to the external hexagon implant design compared to the internal¹⁷⁸.

Pjetursson et al.¹⁴ reported complication rates for abutment and screw loosening and/or fracture of 5.3% and 2.2%, respectively, in FPDs. This was reported as lower in more recent publications^{31,178,297,298}.

The average of abutment or bridge screw loosening varies, according to different reviews, from 0.0%²⁹⁹ to 20.8%¹⁵ for FCDs and from 0.0%²⁹⁷ to 16%⁸¹ in FPDs.

Framework fracture

The incidence of complications of the suprastructure is not a common event and was reported to be 0.54% and 0.24% for the FCD and the FPD respectively¹². However, one review reported a rate of 16.9% after ten years of service for FCDs (Tables 2-3)¹⁵.

Implant fracture

Implant fracture was reported to be a rare event. Adell et al.² reported 3.5% of implant fractures and this rate decreased during the time.

According to Berglundh et al.¹², implant fracture is a rare event that occurred between 0.08% and 0.74% for FCD and FPD, respectively, and this rate did not differ from other publications reported in Tables 2 and 3^{12-15,178,297-299}.

Biological complication

In contrast with technical complications, several biological complications were reported in all studies. Hyperplasia, fistula, mucositis, peri-implantitis and implant loss, among others, are considered as complications with different thresholds that make comparisons among studies confusing. As reported in Tables 2 - 3, total complication rates vary between 0.15% for soft tissue complication¹² to 53.0%⁸¹ for total biological complications in FPDs, and from 0.19%¹² to 35.5%⁸¹ for the FCD.

X-ray analysis and soft-tissues parameters are essential for identifying biological complications and evaluating the health of the peri-implant compartment.

Radiological interpretation of peri-implant bone

The peri-implant bone change with time is analysed using periapical radiographs.

Radiographic analysis facilitates the visualisation of the pre-surgical implant region, and assessment of the bone quantity and quality and, subsequently, the osseointegration for marginal bone alterations with time. Early detection of signs of peri-implant lesions and detection of technical complications are desirable outcomes of the X-rays screening.

To ensure the accuracy and the reproducibility of the measurements, standardised equipment was proposed by Hollender and Rockler³⁰⁶ and subsequently by Strid³⁰⁷ with the use of a radiographic apparatus provided with a collimator, and Eggen Holder to facilitate the position of the film in the patient's mouth parallel to the implant longitudinal axis.

In a study conducted on human cadavers, no statistically significant difference was observed between the actual sizes of implants and the measurements from the periapical projections on X-rays³⁰⁸. However, in experimental model, periapical radiographs were taken at different angulations in implants inserted in models with different alveolar ridge width. The error ranged from 0.1 mm with 1° of angulation to 4.8 mm with 20° of angulation in models with 5 mm and 13 mm of buccolingual width respectively. The authors stated that the reproducibility could be unreliable since it is unlikely that one can obtain repeatable conditions when X-rays are taken on patients³⁰⁹.

Moreover, clinical limitations in the diagnosis occur and are mainly related to:

(i) Possible false negatives in cases of a lack of corticalisation of the bone in the coronal part of the implant. An area of radiolucency around an implant, even if osseointegration is successful, could be present on radiographic films and may be an exaggeration of the clinical reality³¹⁰.

(ii) Possible false positives due to limitations of the two-dimensional view. Crestal bones could appear more radiopaque, covering potential areas of bone resorption mainly in the buccal or lingual side and thus underestimate potential bone loss³¹¹.

(iii) The orientation of the implant may diverge from the perpendicular line of the centrator and threads may not be visible, consequently, the images would not be useful for the analysis³⁰⁹.

(iv) Some anatomical limitations such as the tongue floor in varied reabsorbed mandibles or the palatal vault shapes may limit the procedures in positioning of the film.

In the latter scenario, due to the patient's discomfort and/or pain, a bitewing x-ray could be performed as an alternative. In this procedure, the central beam of the collimator has to remain perpendicular to the longitudinal axis allowing the evaluation of the bone crest. The only limitation of this reliable option is the absence of the apical portion of the implant.

A physical limitation of the observer has to be reported. Humans may not precisely visualise the bright and dark bands that appear in-between the two structures (implant and bone) with opposite intense lighting. This phenomenon, known as the 'Mach-band effect', was described by Ernst Mach (1838-1916) who reported an inhibitory pattern in the neurosensorial system, especially in the retina, which enhances the borders and defines the contours of an object³¹².

Currently, examiners use the digital film and post-production software to modify and better analyse the quality of the bone in a periapical radiograph.

Regardless of the limitation of periapical radiography, it is still the only modality for assessing the osseointegration with time according to various consensus conferences²⁷⁸. An alternative option, such as the cone-beam CT scan, is valid for assessing the pre-operative bone condition but has limited validity in monitoring the peri-implant bone after implant installation³¹³.

Evaluation of the peri-implant bone

There are several acronyms for the description of peri-implant bone and its alterations, such as CBL (crestal bone level or loss), MBL (marginal bone level or loss), MBR (marginal bone resorption)³¹⁴, BL (bone loss or level) BG (bone gain), MBLC (marginal bone level change), MBHC (marginal bone height change) and there might be even more others in use.

To standardise the bone analysis of implants, precise references have to be set depending on the type of implant and its apico-coronal

position at the time of surgery. An bone-level implant, e.g., the AstraTech implant system, is designed to be either placed epi-crestally or slightly sub-crestally^{6,315}. However, if, for any surgical reason, the implant has not completely reached its apico-coronal position, the implant will stay above the crest. Other implants have, instead, a transmucosal design and are placed in a final setting above the bone crest³¹⁶.

For these reasons, the threshold for beginning the analysis of the bone level is the implant/abutment connection reference. The MBL, or CBL, is the bone level distance measured from the implant/abutment reference to the first BIC visible.

Adell et al.² reported that, *'for the different periods and treatment groups, the fixtures were analysed with regard to marginal bone height changes. When 2 or more registrations were performed per year, the mean value of the marginal bone levels was calculated. Loss of marginal bone was measured and related to fixed reference points on each fixture, medially and distally close to the fixture surface'*.

Summarising:

a) MBL represents the distance between the reference point (implant-abutment connection) and the first BIC on the X-ray at a given time. The mean values ((mesial+distal)/2) are reported. If two groups are considered for comparison, a difference between the mean values of each MBL group may be reported.

b) MBL change represents the difference between the mean MBLs of 2-time points. If this difference is negative it represents bone loss, else it represents BG.

MBL change is a mathematical value and does not provide any information on the level of the bone crest at the two-time points considered. (E.g., meaning that an MBL change between time point 1 and 2 reporting a bone loss of 0.5 mm does not provide any data on the MBL at time point 1).

c) Moreover, a difference between the MBL change of the two groups could be calculated for comparative analysis at a certain time.

d) An MBL at the subject level could be evaluated. The sum of the mean MBL values for all the implants in each patient is divided by the number of implants.

To better understand the distribution of each MBL and MBL change in each implant and/or subject, a cumulative curve distribution is often used³¹⁷ (Figures 26-27).

Soft tissue indexes

Clinical investigations are as important as the X-ray analysis to evaluate the peri-implant status with time.

Since there were no precise indications for which index was the most appropriate for evaluating peri-implant tissue status, parameters were borrowed from the periodontal protocols³¹⁸.

In the book '*Tissue-Integrated Prostheses Osseointegration in Clinical Dentistry*' published by Brånemark-Zarb and Albrektsson³⁴, there was no description on how to evaluate the soft tissue parameters.

Adell et al.² reported that gingivitis may cause bone loss with time and they advocated the importance of scheduling patients for regular or even more frequent maintenance, hygiene and/or prophylactic visits as the ones described by Lindhe & Nyman for patients with periodontal diseases³¹⁹.

Probing the soft tissue is claimed to be a routine procedure for analysing the health status of the implant. However, as reported by many authors, the criteria used to analyse the periodontal status, presented with prognostic uncertainties in the evaluation of the 'tonus' in the peri-implant area. Under some circumstances, there are weak correlations between severe index scores and the severities of diseases ascertained through X-ray analyses³²⁰⁻³²³.

Brånemark criticised the use of periodontal parameters for the diagnosis of peri-implant diseases¹.

Two of the most authoritative researchers in the periodontal and implantology fields reported different correlation outcomes between BoP and bone loss in their respective studies in beagle dogs. Ericsson & Lindhe³²⁴ showed BoP in the majority of the healthy implants while Lang et al.³²⁵ reported that in healthy implants, the BoP was absent and only presented in implants with mucositis or peri-implantitis. Similarly, Sanz et al. reported large variations in the BoP scores among clinical studies³²⁶.

There are four major clinical parameters reported in clinical trials: the plaque index (PI), bleeding on probing (BoP), probing pocket depth (PPD), and keratinised mucosa (KM).

Plaque Index

The presence of the plaque was scored with the PI, which was originally the acronym for the periodontal index system defined by Russell³²⁰ and subsequently by Löe & Silness³²⁷ in order to define the periodontal condition around teeth, rated on a scale of nine levels (0-8). In 1964³²⁸ the score level was set on a scale from 0 to 3. The scores represented the following, 0 - absence of plaque deposit, 1 - plaque disclosed after running the periodontal probe along the gingival margin, 2 - visible plaque, and 3 - abundant plaque.

In a previous study on teeth³²⁹ and subsequently on implants³³⁰ the PI was also assessed with a dichotomous variable on the four surfaces at each abutment.

Mombelli and co-authors³³¹ modified the original periodontal index separating the soft tissue analyses status around implants into different indexes. The plaque formation around the marginal area of the implants, according to Mombelli et al.³³¹ (mPII) was scored from 0 to 3 where the scores represented the following: 0 - no detection of plaque, 1 - plaque only recognised by running a probe across the smooth marginal surface of the implant (implants covered by titanium spray in this area are always scored 1), 2 - plaque can be seen by the naked eye, and 3 - abundance of soft matter. Lindquist et al.³³² in 1988 reported a different 3-grade score as follows: 0 - no visible plaque, 1 - local plaque accumulation < 25% of the visible abutment area, and 2 - general plaque accumulation > 25%.

Bleeding on Probing & Probing Pocket Depth

BoP and PPD are parameters registered with the use of a periodontal probe.

BoP is considered as a potential inflammation status of the peri-implant tissue. The BoP was described as a dichotomous variable with '1' as the presence of bleeding within 15 seconds after probing³³³. Mombelli et al.³³¹ modified the Muhlemann & Son's index with the sulcus Bleeding Index (mBII) which was assessed as follows: '0' when there is no bleeding when a periodontal probe is passed along the gingival margin adjacent to the implant), '1' when isolated bleeding spots are visible, '2' when blood forms a confluent red line on the margin, and '3' heavy or profuse bleeding.

Apse et al.³³⁴ proposed a different 4-score scale for assessing the marginal mucosa status around implants. The score is '0' for normal mucosa, '1' for a minimal inflammation with colour change and minor oedema, '2' for a moderate inflammation with redness, oedema, and glazing), and '3' for severe inflammation with redness, oedema, ulceration, and spontaneous bleeding without probing.

The PPD, in an implant unit restoration, is defined as the distance between the apical portion of the pocket and the mucosal margin. The measurement is quantified with a calibrated probe that has to be inserted gently in the tissue.

However, if it is stated that probing the peri-implant tissue should be an essential diagnostic tool, its procedure presents two-fold methodological limitations:

(i) The first is qualitative, and is related to the diagnostic instrument. It is known, among clinicians that probing an implant is not easy. Under some circumstances, the bulky framework obstructs the insertion of the instrument; the geometry of the prostheses, especially, with a convex contour and/or over contour design could create a barrier limiting the probing procedures in the mucosal sulcus²⁹¹. This condition could also be aggravated by the three-dimensional anatomical position of the implant and the presence of a width tissue, in some areas, which could reduce the insertion of the tool. Serino and Ström³³⁵ reported 48% of peri-implantitis in patients with improper prosthetic design compared to 4% in those with an optimal design.

This increases the likelihood of false positives or negatives since different pressures are imposed on the probe. Mombelli et al.³³⁶ analysed the different pressures (0.25 N to 1.25 N) in the periodontal and peri-implant sulci. The authors concluded that the measured depth of the peri-implant sulcus is subjected to more pressure than the periodontal sites, and the variation is higher when a lower force range is applied (0.25 N to 0.50 N). This was confirmed by Gerber et al. in 2009³³⁷. The authors reported that bleeding is associated with pressure. A slight increase in probing from 15 N to 25 N increased the BoP by 14%.

(ii) The second limitation is quantitative. Every clinician could report if there is no bleeding (score: 0) or abundant bleeding (score: 3), according to the modified Mombelli score³³¹. However, identifying differences between scores 1-2 and 2-3 may be challenging. The

probing procedures may also slightly provoke trauma, which results in bleeding.

The use of calibrated probes to limit biased interpretations or, in case of clinical trials, a possible inter- and or intra-examiner calibration are valid solutions for this limitation³³⁸.

Keratinised mucosa

The KM, also termed ‘attached’ mucosa, is measured from the gingival margin to the mucogingival junction.

The KM was claimed to be associated with the peri-implant tissue status; however, the effectiveness of its role is under debate. Even if it was reported that a lack of keratinised mucosa was associated with less favourable peri-implant conditions³³⁹, in a recent retrospective study it was reported that the width of KM was not correlated with MBL, BoP, or PPD³⁴⁰. However, the KM was claimed to be helpful for the patient during maintenance¹⁷⁴.

PATIENT'S PERCEPTION

'The quality of life is determined by its activities'

Aristotle (384 BC – 322 BC) Philosopher

According to the World Health Organisation (WHO), *'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'*³⁴¹. Consequently, the status of health cannot be determined only by physical parameters alone³⁴².

In dentistry, oral health and its implications for the quality of life, OHRQoL, has been widely debated and should be of paramount importance to every clinician, especially for understanding patient perspectives³⁴³⁻³⁴⁵.

Following the advent of dental implants, better attention has been given to the outcomes of oral rehabilitation and their effects on the quality of life³⁴⁶, especially when the WHO, in 2001, reported edentulism as a physical handicap with several limitations.

A clinical implant-prosthetic success may not sufficiently address the patient's expectations. Understanding the patient's needs and educating him/her on the benefits of certain treatments is not an easy task. Consequently, researchers have analysed the importance of patient perceptions during treatment to provide the most appropriate therapy options³⁴⁷.

Several approaches have been used to investigate patient OHRQoL and satisfaction. There are still numerous investigations into the instruments that are best suited for understanding patient outcomes³⁴⁸. However, there are significant limitations in this area since psychometric evaluation may not be sensitive enough. Quality

assessments could be limited because patients cannot test different treatments³⁴⁹.

According to a study by Heydecke et al.³⁵⁰, 9 out of 13 patients preferred IOD to an FCD after testing both solutions. The patients preferred the removable option since it was considered better in chewing performance and easier to clean compared to the fixed one. However, this kind of clinical research cannot be applied routinely in clinical practice because of the associated costs.

Moreover, even if a patient could test and choose the most appropriate treatment, resulting in an increased OHRQoL, he/she could still not be completely satisfied³⁵¹.

Patient-reported outcome measures (PROMs) have been of major interest within the last 2 decades³⁵², and were defined in 2012 during the VIII European Workshop on Periodontology as 'subjective' reports of patients' perceptions of their oral health status and its impact on their daily life or quality of life³⁵³. Researchers are increasingly using PROMs to assess patients' needs, desires, and satisfaction with oral health status³⁴⁹.

The most used PROM is the Oral Health Impact Profile (OHIP). The OHIP was ideated by Slade in 1994³⁵⁴, and is a questionnaire that measures the effect of oral diseases on the perception and well-being of patients using the theoretical model of oral health formulated by Locker³⁵⁵. The 49 questions in the OHIP (OHIP-49) address seven topics (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap) before and after treatment. Each answer has a 5-point score based on the Likert scale³⁵⁶.

RCTs showed a significantly improved OHRQoL of patients rehabilitated with IODs compared to CD dentures using the OHIP-49 questionnaire^{357,358}. Other trials also used OHIP-49 to assess the effect on the quality of life in patients with IODs and FCDs, and reported improvements compared to CD; however, no difference was found between the effects of the two implant retentive options (IOD and FCD)^{348,359}.

Slade developed a shorter version of OHIP-49 in 1997, 3 years after the original questionnaire was published, with only 14 questions (OHIP-14). In the same article, the author tested its reliability, validity, and precision, allowing researchers to use it in their clinical studies to

quantify satisfaction during treatment³⁶⁰, especially the rehabilitation of edentulous patients³⁶¹⁻³⁶³.

In a recent systematic review published by Yao et al.³⁴⁸ it has been explained that measuring the quality of life with a PROM instrument is not the same as defining the satisfaction of the patient examined.

Satisfaction is achieved when the patient's expectations are completely met. However, it is dependent on patient's characteristics such as (i) the age or educational attainment; (ii) influence of the environmental, and (iii) socio-psychological phenomena, such as self-interest (the Hawthorne effect) and setting of the treatment (university or private centre)^{351,364}. Other validated questionnaires were used, in the meantime, for the psychometrical analysis of the treated patient³⁶⁵⁻³⁶⁷.

Other authors used a modified version of the OHIP-14 since they claimed that the original format did not evaluate some basic parameters related to prosthetic rehabilitation³⁶⁸.

There are several questionnaires and tools reported in literature and there are no standardised and comparable assessments of the quality of life for patients in clinical research, and the need for guidelines is urgent for the scientific community³⁴⁸.

AIMS

The general aim was to provide insights into the risk of complications in screw-retained multi-unit frameworks manufactured using the CAD-CAM technique.

The specific aims were as follows:

1. to assess the effects of misfit at implant-level FPDs and supporting bone levels on the generation of implant cracks (**study I**);
2. to evaluate the hard and soft tissue changes in implant-supported FPDs in an implant or abutment connection level set-ups (**study II**);
3. to evaluate the MBL change and soft tissue parameters in FCDs and IODs (**study III-IV**);
4. to report patient's satisfaction when treated with implant-supported FCDs and IODs (**study III-IV**); and
5. to analyse the technical and biological complications of screw-retained CAD-CAM frameworks (**study II-III-IV**).

MATERIALS AND METHODS

Target Population

Fifty patients were treated with 118 implants in one centre in **Study II**.

Fifty-six patients were treated with 280 implants in three centres in **Study III**.

Forty patients were treated with 185 implants in five centres in **Study IV**. (Table 4, see next page)

Implant system

In this thesis, the AstraTech Implant System (Dentsply Sirona Implants, Mölndal, Sweden) was adopted. Two types of implants were used, the OsseoSpeed™ TX (TX) (**Study I, II, and IV**) and OsseoSpeed™ EV (EV) (**Study II-IV**).

Abutment components (Uni-abutment)

The screw-retained index-free abutments with two different angulations, varying with implants, were used in the clinical trials included in this thesis.

The Uni Abutment 33° (Uni Abutment 33° EV Dentsply Sirona Implants, Mölndal, Sweden) was used on the AstraTech EV implant (**Study II-IV**) and the Uni Abutment 45° (Uni Abutment 45° TX Dentsply Sirona Implants, Mölndal, Sweden) was used on the AstraTech TX implant (**Study III-IV**).

Table 4. Description of sample size and components reported in each study.

	Patients N.	Implants N.	Implant type	Abutment components	Interface Connection	Framework Material	Fixation Type	Prosthesis Material
Study I		32	OsseoSpeed™ TX		Implant Level	Titanium	screw-fixed	
Clinical Studies								
Study II	50	119	OsseoSpeed™ EV	Uni Abutment 33°	Implant or Abutment Level	Cobalt-Chrome	screw-fixed	Ceramic
Study III	56	280	OsseoSpeed™ TX	Uni Abutment 45°	Abutment Level	Titanium	screw-fixed	Resin/Composite
Study IV	40	185	OsseoSpeed™ TX/EV	Uni Abutment 45/33°	Abutment Level	Titanium	screw-fixed/removable	Resin/Composite
Total (II+III+IV)	146	584 + 13						

Frameworks

The frameworks used in all the studies were manufactured by Dentsply Sirona (Atlantis Superstructures, Dentsply Sirona Implants, Hasselt, Belgium). In **Study I, III and IV** the frameworks were milled (SM) with Ti material; in **study II** the framework was laser sintered (AM) welded on milled (SM) connection interface in Co-Cr.

Mechanical Fatigue Test (Study I)

Setting: a mechanical cycling loading test was performed using an experimental model consisting of two parallel implants with a diameter of 3.5 mm and a length of 11 mm (OsseoSpeed TX, Astra Tech Implant System, Dentsply Sirona Implants, Mölndal, Sweden). The implants were embedded in epoxy resin cylinder with a diameter of 10 mm and a length of 13 mm and firmly seated in an aluminium block (60 × 60 × 40 mm) simulating an implant-supported bridge.

Two metal blocks were manufactured to mimic the no-misfit and the misfit condition, defined as the discrepancy between the implant longitudinal axis and the restorative longitudinal axis, as follows:

- No-misfit: the distance between the center of the two implants was 35.0 mm¹⁹⁸.
- Misfit: the distance between the center of the two implants was 35.2 mm.

Moreover, to detect the effect of supporting bone level, implants were placed with different embedding depths:

- No bone loss: the implant shoulder was placed at 0.0 ± 0.5 mm above the surface of the epoxy resin (nominal level).
- Bone loss: the implant shoulder was placed at 3.0 ± 0.5 mm above the nominal level according to ISO standard 14801:2007³⁶⁹, simulating the worst bone loss scenario.

Sixteen milled Ti bridge type rigid frameworks (42 × 10 × 7.5 mm) were fabricated from the same file. The distance between the center of the two implants was 35 mm¹⁹⁸. The accuracy of the frameworks was granted by CNC-milling manufacturing, which was demonstrated to have small variability and high precision with an amount of error of less than 10µm^{233,370}. The total length of the conical connection was 2 mm, and the depth of the framework into the implant was 1.2 mm.

The frameworks, free from antirotational interlocking, were screwed with a torque of 20 Ncm into the implants. Radiographs were taken after the final position of the framework to check the presence of misfit. Experimental models (n = 16) were subdivided into 4 groups based on the misfit condition and the supporting bone condition, as shown in Figure 5.

Figure 5. Experimental models subdivided into 4 groups based on implant vertical position and misfit: (a) misfit/no bone loss, (b) misfit/bone loss, (c) no-misfit/no bone loss, and (d) no-misfit/bone loss. Arrow represents the direction of the loading. **(Study I)**

Test

The framework was externally dynamically loaded vertically in the center using a loading machine (Electropuls E3000, Instron) with a force of 160 to 1,600 N at 15 Hz for 1×10^6 cycles. The rigidity of the framework minimizes unfavourable bar deformation, inducing an equal vertical load and negligible bending moment to the implant-

abutment interface. Therefore, the expected dynamic load on each implant varied between 80 N and 800 N.

Analysis

After loading, the embedded implants were removed from the metal block and examined through an optical microscope with $\times 50$ magnification (ZEISS Stemi 2000-C Stereo Microscope).

Afterward, the samples were investigated using a scanning electron microscope (SEM) (Hitachi TM3000, Hitachi). Implants were placed in a tilted fashion into the vacuum camera. Each implant was rotated 60 degrees and analysed three times to obtain a complete view of the conical inner side (Figure 6).

Figure 6. (A) Implant placed in a titled fashion into the vacuum camera of the SEM. Each implant was rotated 60° and analysed 3 times to obtain a complete view of the conical inner side. (B) SEM image of the implant. (**Study I**)

As a final examination, the samples were analysed with an industrial computed tomography three-dimensional (CT-3D) X-Ray Measuring System (ZEISS Metrotom 800 CT system). The measurement conditions were set at 95 kV and 80 μ A. The primary X-ray beam was filtered by a 0.5 mm thick aluminium target. 850 high-resolution (scan resolution of 10.17 μ m, voxel dimension) radiographs were collected, by spinning the sample in autofocus mode, in no more than 60 minutes. Special software (Volume Graphics) was used to reconstruct the two-dimensional (2D) images into a 3D volume (Figure 20).

Finite Element Analysis (Study I)

Setting

To investigate the stress distribution at the implant, finite element models, representing the setups in mechanical fatigue tests, were developed in ANSYS 18.2 (ANSYS Inc., Canonsburg, USA).

Taking advantage of the symmetry of the model, only one implant side was simulated (Figure 7). To capture the mechanical properties of the metallic components, the simulations were performed using multilinear material properties (Figure 8).

This model captures the increase in stress between yield and UTS. In addition, this material model limits the simulated stress to the ultimate stress³⁷¹. The interface between the framework and the implant was modelled with a friction coefficient of 0.3³⁷². To reduce the simulation time, the interface between the framework and the abutment screw was modelled as a frictionless connection, while the interface between the implant and support material was modelled as a bonded one.

The meshes were generated using the ANSYS default settings with a denser mesh size of 0.075 mm in the implant-framework interface. These settings resulted in 0.13×10^6 nodes and 0.08×10^6 elements of the bone loss condition and 0.19×10^6 nodes and 0.12×10^6 elements of the no bone loss condition.

To analyse how the mesh density affected the results, the model that comprised a misfit of 0.2 mm and 0 mm bone loss was modelled with an increased mesh of 0.05 mm and with a reduced mesh of 0.1 mm at the implant-framework interface.

Figure 7. FEA model simulated for one implant side. **(Study I)**

Figure 8. Multilinear material properties. **(Study I)**

Tightening of the framework was simplified in the FEA model to only include a screw preload of 250 N and neglecting any shear forces arising due to screw torqueing³⁷³. This simplification does not suppose to affect the results in the coronal part of the implant. To replicate the experimental setup, the preload was applied first and thereafter, a maximum load of 800 N was applied on the implant at the implant-framework interface.

Analysis

The stress levels were analysed by the mean von Mises stress criterion. The alternating stress range (σ_r) was defined as the difference in von Mises stress between 800 N (maximum stress level $\sigma_{\max}$) and 80 N (minimum stress level $\sigma_{\min}$):

$$\sigma_r = \sigma_{\max} - \sigma_{\min}$$

The alternating stress amplitude (σ_a) was defined as:

$$\sigma_a = \sigma_r / 2.$$

The mean stress level (σ_m) was defined as:

$$\sigma_m = (\sigma_{\max} + \sigma_{\min}) / 2.$$

In this simulation, the modified Goodman theory was used to assess fatigue³⁷¹. The mean stress correction by Goodman results in an effective fully reversed stress amplitude (σ_{er}) that can be used to compare with an existing stress life diagram (S-N) of fully reversed load ($R = -1$) of titanium grade 4:

$$\sigma_{er} = \sigma_a \times \left(1 - \frac{\sigma_m}{\sigma_u}\right)$$

where σ_u is the UTS of the material²⁵². The effective fully reversed stress amplitude σ_{er} found in this simulation was compared with a stress-life diagram (S-N) of titanium grade 4 with a UTS of 820 MPa, reflecting the mechanical properties of the implant used in the *in vitro* fatigue test. The S-N curve of Ti grade 4 with UTS of 820 MPa used in this study was derived from an offset of the S-N curve of Ti grade 4 with a UTS of 470 MPa presented by Chandran (Figure 9)²⁵³. The offset was calculated as the ratio between UTS 820 and UTS 470.

Figure 9. Stress-life diagram (S-N) of Ti grade 4 with a UTS of 820 MPa, reflecting the mechanical proprieties of the implant used in the *in vitro* fatigue test. The S-N curve of Ti grade 4 with UTS of 820 MPa (orange line) was derived from an offset of the S-N curve of Ti grade 4 with a UTS of 470 MPa (blue dots)²⁵³. **(Study I)**

Clinical Studies (Study II-III-IV)

Ethical Aspects and Study Design

The clinical studies were performed undertaking the Helsinki declaration³⁷⁴ and were approved by Medical Ethics Committee: (Study II ‘Azienda Ospedaliera di Circolo’, Italy (VA) n. 0001832); (Study III ‘Azienda U.L.S.S. N.16’, Italy (PD) n.14161); (Study IV ‘Azienda Ospedaliera di Circolo’, Italy (VA) n. 000205-35815).

Study II and III were prospective randomized trials while Study IV was a prospective cohort study. Study II and III were registered at the U.S. National Institutes of Health (Clinicaltrials.gov) (n: NCT02789956 for Study II and n: NCT02405169 for Study III) and followed the CONSORT 2010 as a guideline to report on the outcomes³⁷⁵ (Figures 10-11).

Figure 10. Consort flow diagram. (Study II)

Study Hypothesis

The null hypothesis of **Study II** was that there is no difference in hard and soft tissue changes as well as no difference in prosthetic complications between the group of patients treated with an IL and the group of patients treated with an AL screw retained FPD.

The null hypothesis of **Study III** was that 4-I group performs, in terms of MBL change of the implants, as well as the 6-I group in rehabilitating patients with edentulous maxilla.

Study Centres

The clinical studies were conducted at different centres.

Study II was a randomized trial conducted in one center located in Busto Arsizio, Italy (VA) and the clinician (MT) is affiliated to Malmö University (Malmö, Sweden).

Study III was conducted in three private clinics located in the north area of Italy. One center (clinician, MT) is located in Busto Arsizio, Italy (VA). One center is located in Poiana Maggiore, Italy (VI)

Figure 11. Consort flow diagram. (Study III)

and one center is located in Padova, Italy (PD) and the respectively clinicians (EC)(DC) are affiliated to FRANCI Institute (Padova, Italy).

Study IV was conducted in 5 private centres located in Italy. One center (MT) is located in Busto Arsizio, Italy (VA). One center is located in Poiana Maggiore, Italy (VI). One center is located in Padova, Italy (PD). One center is located in Fiorano Al Serio; Italy (BG) and one center is located in Catania, Italy (CT) the respectively clinicians (VF)(PT) are affiliated to FRANCI Institute (Padova, Italy).

At each center the clinician has more than 15 years of experience on the implant system used in these trials.

Patients Selection

Patients were selected to be included in the clinical studies based on the following criteria: age ≥ 18 years; absence of systemic medical condition: patients had to be healthy (ASA-1) or presented mild systemic disease (ASA-2)³⁷⁶; good oral hygiene defined as full mouth plaque score $\leq 25\%$ ³⁷⁷.

Additional inclusion criteria were applied on each study and in particularly patients were included in **Study II** with at least two adjacent teeth to be replaced in any quadrant of the jaws.

Patients were included in **Study III** with: (i) edentulous maxilla or having remaining teeth that were intended to be extracted; (ii) sufficient amount of bone (6 mm or more) in the recipient site to allow the placement of at least 6 implants without bone augmentation procedures.

Patients were included in **Study IV** with a vertical distance between the two arches sufficient to support the milled framework according to the framework design specifications as reported in a further section.

Patients were excluded from the studies based on the following criteria: implant-treated patients with bone defects in need of major bone augmentation; patients with bone defects resulting from tumour resection; smoking more than 10 cigarettes per day; severe renal and liver disease; history of radiotherapy in the head and neck region; chemotherapy at the time of the surgical procedure; uncontrolled diabetes; mucosal disease (such as oral lichen planus and epidermolysis bullosa), in the areas to be treated; non-compliant patients; situations that the main investigator considered unsuitable for the surgical treatment.

Moreover, in **Study III** and **IV** were excluded patients with severe malocclusion skeletal class III or class II deep-bite patients which required orthognathic surgery

The patients that met the above reported criteria, were informed orally and asked to sign a written informed consent. The enrolled patients of **Study II** and **III** were randomly allocated to each group.

Randomisation

In **Study II**, the randomisation was performed before the second stage surgery and each patient was distributed to the allocated group according to a computer randomisation block software.

In **Study III**, the randomisation was performed before the first surgical procedure on the day of the implant installation. Each patient was assigned to the allocated group according to a manually generated restricted list and sealed opaque envelopes.

Study Participants

Study II: 50 patients (21 males, 4 smokers), with a mean age of 58.9 years at the day of surgery (range 35.6-93.5) were treated between January 2015 and October 2016. After the randomization the IL group included 25 patients (17 females, 3 smokers), with a mean age of 57.3 years (range 41.4-73.2) while the 25 patients (13 males, 1 smokers) of the AL group presented a mean age 65 years (range 35.6-93.5).

As opposite dentition, 34 patients (68%) presented natural dentition; 8 patients (16%) had natural dentition and implant and 8 patients (16%) had implant supported bridges.

Study III: 56 patients (30 females, 9 smokers) with mean age of 67 years at the day of surgery (range 48-89) were treated between April 2013 and September 2015.

28 patients (17 males, 3 smokers), with a mean age of 64.6 years (range 51-81) were included in the 4-I group while 28 patients (19 females, 6 smokers), with a mean age of 69.6 years (range 48-89) were included in 6-I group. As opposite dentition, 22 patients (39.3%, 11 in each group) presented FCPs in the mandible; 15 patients (26.8%, 6 in the 4-I group and 9 in the 6-I group) had natural dentition; 14 patients (25%, 8 in the 4-I group and 8 in the 6-I group) had fixed partial prostheses on implants in the posterior regions and natural dentition in the frontal area, 4 patients (7.1%, 2 in each group) presented natural dentition in the frontal area and removable denture in the posterior segments of the lower jaw; 1 patient (1.8%, in the 4-I group) had an overdenture on two implants in the mandible.

Study IV: 40 (21 males, 4 smokers), with a mean age of 69 years (range 49-88) were treated between February 2014 and April 2016.

As opposite dentition 11 patients (27.5%) presented natural dentition plus fixed partial denture teeth supported; 7 patients (17.5%) presented IOD; 7 patients (17.5%) presented a CD; 6 patients (15%) presented a FCD; 4 patients (10%) presented complete natural dentition; 3 patients (7.5%) presented natural dentition plus

fixed partial denture implants supported; 2 patients (5%) presented a partial denture supported by teeth.

First-Stage Surgical Procedures

In **Study II, III and IV** each patient received antibiotic prophylaxis (Amoxicillin 2 gr) 1 hour prior to implant placement (IP). A different antibiotic was prescribed for the penicillin-allergic patients. Patients rinsed chlorhexidine 0.2% for 1 minute prior to surgery and local anaesthesia was induced. After a crestal incision, a full thickness flap was elevated. In **Study III and IV** the antibiotic therapy was continued after surgery, 2 gr twice a day for 6 days.

In **Study II**, 2, 3, or 4 implants were placed in each patient according to the drilling protocol described by Toia et al.³⁷⁸. The implant bone site was classified according to L&Z classification³⁷⁹ and ITV was registered using SA-310 W&H Elcomed implant unit (W&H, Burmoos, Austria). After the positioning of the cover screw, suturing was performed with primary adaptation of the flaps by means on accurate suture using absorbable 5-0 suture (Vicryl, Ethicon J&J International, St-Stevens-Woluwe, Belgium).

The IL group was treated with 58 implants while the AL group was treated with 61 implants. Sixty-six implants were placed in the mandible and 53 in the maxilla. Implants diameter and length are as follows: 3.6×6mm (5); 3.6×8mm (9); 3.6×9mm (17); 3.6×11mm (5); 3.6 × 13 mm (8) ; 4.2 × 6 mm (1); 4.2 × 8 mm (11); 4.2 × 9 mm (18); 4.2 × 11 mm (11); 4.2 × 13 mm (5); 4.2 × 15 mm (2); 4.8 × 6 mm (3); 4.8 × 8 mm (4); 4.8 × 9 mm (7); 4.8 × 11 mm (5); 4.8 × 13 mm (1); 5.4 × 8 mm (1); 5.4 × 9 mm (3); 5.4 × 11 mm (2); 5.4 × 13 mm (1).

In **Study III** implant sites were prepared and, after randomization, 4 or 6 fixtures were positioned in the maxilla and the 4-I group patients received 112 implants while the patients of 6-I group were treated with 168 implants. Implants diameter and length are reported in Tables 5 - 6.

The stability of the implant was registered manually during the insertion of a cover screw. If during counter-clockwise rotation of the cover screw the implant moved together with the screw, the implants were registered as 'spinning'. Otherwise, the implant was registered

as ‘stable’. Nine implants (6 in the 4-I group) demonstrated reduced stability at the installation.

According to the native bone availability, if the distal implants needed to be tilted, they were inclined parallel to the mesial wall of the sinus¹³¹. After the positioning of the cover screw, primary adaptation of the flaps was obtained, and the flaps were sutured.

Table 5. Implants diameter specifications in each group.

Note: diameter is expressed in mm; 4-I (four-implants); 6-I (six-implants). (Study III)

Group	Diameter				Total
	3.5	4	4.5	5	
4-I	20	82	6	4	112
6-I	60	67	31	10	168
Total	80	149	37	14	280

Table 6. Implants length (mm) specifications in each group.

Note: length is expressed in mm; 4-I (four-implants); 6-I (six-implants). (Study III)

Group	Length						Total
	6	8	9	11	13	15	
4-I	0	11	17	53	31	0	112
6-I	3	13	32	60	50	10	168
Total	3	24	49	113	81	10	280

In **Study IV** implants were placed in the mandible and in the maxilla according to the treatment plan.

Each operation was finalised by performing a passive primary adaption of the flaps to obtain a full periosteal cover of the implant cover screws, and then the flaps were sutured.

Patients were treated with a total of 185 implants. Twenty-five patients (62.5%) were treated in the mandible. Each patient received an average of 4.65 ± 1.2 implants (range 4 to 8 implants) and 100 implants (54.3%) were placed in the mandible. 120 implants (65%) were TX (Astra Tech Implant System OsseoSpeed TX, Dentsply Sirona Implants, Mölndal, Sweden), and 65 (35%) were EV designs (Astra Tech Implant System OsseoSpeed EV, Dentsply Sirona Implants, Mölndal, Sweden). TX Implants diameter and length were: 3.5 X 8mm (3); 3.5 X 9mm (9); 3.5 X 11mm (19); 4.0 X 6mm (6); 4.0 X

8mm (2); 4.0X 11mm (45); 4.0 X 13mm (26); 4.5 X 11mm (2); 4.5 X 13mm (4); 5.0 X 9mm (1); 5.0 X 13mm (3). Implants EV diameter and length are here reported: 3.0 × 8 mm (2); 3.6×6mm (3); 3.6×8mm (1); 3.6×9mm (1); 3.6×11mm (8); 3.6 × 13 mm (5); 4.2 × 9 mm (9); 4.2 × 11 mm (27); 4.2 × 13 mm (9).

The patients were instructed to rinse with chlorhexidine 0.12% daily for 15 days and were advised to take nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief if needed. In **Study III** and **IV**, antibiotic therapy was continued after surgery, 1 gr twice a day for 6 days and patients were instructed not to wear the CD for two weeks after surgery. Thereafter, the CD were relined and the patients could wear them until the second stage surgery. During the healing phase patients were recommended to follow a soft diet.

Second-stage Surgical Procedures

In each clinical study implants were placed with two stage procedures and the second surgery was performed after 6 weeks in **Study II** and after 8 ($\pm$ 2) weeks in **Study III** and **IV** according to the healing time suggested by the implant company.

In **Study II**, after the randomization, in the AL group, the cover screws were removed from the implants and a screw-retained index-free abutment was seated and secured using a torque wrench at 25 Ncm. The abutments were divided into 3 lengths: 21 abutments of 1 mm, 33 abutments of 2 mm and 7 abutments of 3 mm. A healing cap (Uni Abutment EV Heal Cap Dentsply Sirona Implants, Mölndal, Sweden) was positioned onto the abutment. In the IL group, the cover screws were replaced with healing abutments (Healing abutments, Heal Design^(TM) EV, Dentsply Sirona Implants, Mölndal, Sweden).

In **Study III**, after second surgery, 1 implant in the 6-I group failed and the treatment for the patient continued on 5 implants. All the 279 remaining osseointegrated implants were connected to an external screw-retained index-free abutment that was seated and secured at 20 Ncm using a manual torque wrench. The abutment height was selected clinically depending on the thickness of the mucosa or/and depending on the available inter-occlusal space and divided in five lengths: 0.5, 1, 2, 4 and 6 mm (Table 7).

Trans-mucosal healing caps (ProHeal Cap, Dentsply Sirona Implants, Mölndal, Sweden) were seated onto the abutments.

In **Study IV**, implants were uncovered and screw-retained index-free abutment with different heights as presented in **Study II** and **III** were seated and secured. Sutures were applied in each patient if necessary.

Table 7. Abutment length specifications in each group.

Note: length is expressed in mm; 4-I (four-implants); 6-I (six-implants). (**Study III**)

	Abutment Length					Total
	0.5	1	2	4	6	
Group						
4-I	12	28	60	8	4	112
6-I	4	23	118	17	5	167
Total	16	51	178	25	9	279
%/Total	5.7	18.3	63.8	9	3.2	100

Prosthetics Procedures

Similar prosthetics procedure were used in all the studies. Impression were taken after 1 week in **Study II** and after 2 (± 1) weeks in **Study III** and **IV** from abutment connection. A customized impression tray was fabricated and silicone elastomeric dental impression material (Aquasil Ultra, Dentsply-Sirona, Milford, Connecticut) was used in **Study II** and a polyether material (ImpregumTM 3M Oral Care, St. Paul, MN, USA) was used in **Study III** and **IV**. A non-splinted technique was used³⁸⁰.

The technician poured the master model and produced both a gypsum index, connecting temporary index-free abutments to validate the model, as well as a wax-up. The gypsum index was seated and screwed. In **Study II**, its final position was checked with a periapical radiograph. In case of fracture of the index, a new impression was taken, and a new index was produced and checked again in the patient's mouth. This step was mandatory to validate the master model.

The wax-up was regulated according to the occlusion, phonetics, lip support and the vertical dimension of the patient³⁸¹. The master model and the anatomical wax-up were sent to the milling center. The model and the wax-up were scanned, and a virtual digital superstructure design was produced and uploaded in the software for final review and approval prior to fabrication³⁸².

After 4($\pm$ 2), 6($\pm$ 2) and 8($\pm$ 2) weeks from the impression in **Study II, IV and III** respectively, the definitive screw retained implant supported multi-unit restoration was installed and was considered as baseline timepoint (BL). The screw-retained index-free abutments of all the studies was secured using a torque wrench before seating the framework.

The summary of the number of implants in each patient and number of FPD units in **Study II** is reported in Table 8.

The screw access holes were closed with polytetrafluoroethylene (PTFE) and composite in **Study II** and **III**³⁸³.

Table 8. Summary of the number of implants in each patient and number of FPD units.

Note: IL (implant level); AL (abutment level). (**Study II**)

Implants N.	Patients			FPD Units				
				2	3	4	5	6
	2	35	IL 20 AL 15	14 11	6 4			
3	11	IL 2 AL 9		1 3	1 4		1 1	
4	4	IL 3 AL 1			1 2 1			
Total	50	50	25	14	6	4	1	

Framework design specifications

In **Study II**, frameworks, to be finalize with ceramic, were produced in Co-Cr with an AM process on the milled implant connection interface³⁸⁴ (Figure 12).

In **Study III** frameworks, to be finalize with resin teeth or composite, were fabricated in Ti. The framework was produced with retentive surface and retention elements trough virtually a cut-back process designed based on the diagnostic set-up. Each full-arch maxillary framework was planned to support 12 teeth from the first right molar to first left molar, giving a teeth-implant ratio of 3 and 2 in the 4-implant and 6-implant group respectively.

In cases distal cantilevers were included, their length depended on the span between the implants, amount of vertical and transversal space, the position of the holes and opposite arch dentition (Figure 13-14).

Figure 12. Co-Cr framework with an additive manufacturing (AM) process on milled (SM) implant connection interface. **(Study II)**

Figure 13. Figures of a patient belong to the 4-implant group with x-rays at Baseline (BL), 1-year (1Y) and 3-year (3Y). A) Surgery. B) Healing of the soft tissue at baseline (BL). C) Titanium milled framework. D) Frontal view at BL. E) Frontal view at 3Y. **(Study III)**

Figure 14. Figures of a patient belong to the 6-Implant group with x-rays at Baseline (BL), 1-year (1Y) and 3-year (3Y). A) Surgery. B) Healing of the soft tissue at baseline (BL). C) Titanium milled framework. D) Frontal view at BL. E) Frontal view at 3Y. **(Study III)**

In **Study IV** the characteristics of the design comprised two CAD-CAM milled titanium bars for overdenture. The mesostructure was a fixed screw-retained bar on abutment level set-up. In some cases, where at least 6 implants were present, the mesostructure bar was milled in two pieces. The suprastructure represented the female counter-bar that was incorporated in the removable denture and was milled with additional retention pins to enhance the adhesion during the finalization with custom teeth or denture resin³⁸⁵⁻³⁸⁷.

The retention between the two bars was guaranteed by the frictional force obtained by an angle of 4° conical design of the mesostructure. Additional retention elements (Ceka M2/M3; Rhein 83 equator/micro; Bredent locking pin) could be included in the mesostructure, with its male portion, and in the suprastructure, with the correspondent female counterpart, to increase the stability, according to patient's characteristics and to be mouldable according to patient's requests³⁸⁵.

The two Ti bars requested at least a minimum vertical space of 5 mm and a minimum of transversal space of 4 mm. These values were dependent on several circumstances such as span between the implants, cantilever length, type and amount of attachments and opposite dentition (Figure 15).

Figure 15. Clinical case of **Study IV** with 4 implants in position in the mandible (A). Mesostructure, milled in one piece, directly screwed on abutment level connection with retention elements (Gold Colour) (B). Suprastructure inserted inside the denture with retention frictional elements (C). Final removal prosthesis in situ with a set-up of 12 teeth (D). X-ray evaluation of the final prosthesis where both the primary and secondary structures are evident (E). The frictional elements are present in the posterior segments (red arrows). It is visible in the suprastructure the retention pins (I-shape).

The numbers of teeth (units) of the overdenture's prostheses were 11 units in 4 patients (10%), 12 units in 27 patients (67%) and 14 units in 9 patients (23%). Two patients (4%) presented a mesostructure with 2 bars (Figure 16) while 38 patients (96%) presented one milled bar (Figure 15).

The retention pins were milled with an I-shaped (Figure 15) in 9 and with a T-shaped (Figure 16) in 31 suprastructures, (23% and 77% respectively).

Figure 16. Digital steps during the production of the framework a case of **Study IV**:

- (A) Model mock-up scanned with a set-up of 14 teeth.
- (B) Suprastructure (hybrid counter-bar) with retention pins (T-shape)
- (C) Mesostructure milled in two pieces.

Follow-up Protocol

After the delivery of the final restoration, each patient received a careful hygiene and motivational instruction and was recalled for professional cleaning twice a year. The examination visits were set depending on the study.

In **Study II** clinical measurements and X-rays examinations were performed at the implant placement and at BL after the delivery of the final restoration. The same examinations performed at baseline were conducted at 6 months and 1-year. In **Study III** the clinical measurements were conducted at BL immediately before the installation of the definitive FCDs and at 1-year and at the 3-year visits after having unscrewed and removed the prostheses. In contrast to this, the X-ray examination was conducted after having seated and secured, with torque wrench control, the prostheses.

In **Study IV**, the same examinations were conducted with the same methodology used in **Study III** but the follow-up visit was to take place after two years.

Clinical Examination

PI, BoP and PPD were registered in all three clinical studies while the presence of KM was examined and registered in **Study II** and **III**.

PI and BoP was registered at each implant site on four surfaces (buccal, lingual/palatal, mesial, distal) in **Study II** and **III** in accordance with Mombelli et al.³³¹.

In **Study IV** the PI and the BoP were registered as a dichotomous variable. In all three clinical studies the PPD was registered with a periodontal probe (PCP 15; Hu-Friedy Manufacturing Co, Chicago, Illinois) by measuring the distance in mm (approximated to the nearest 0.5 mm) from the peri-implant mucosal margin to the bottom of the mucosal pocket.

The KM was measured from the gingival margin to the muco- gingival junction and was registered in **Study II** on four implant sites (mesial, buccal, distal, and lingual/palatal) and only in the buccal aspect in **Study III**.

The KM was assessed as follows: '0' when there was an 'absence' of KM meaning that the gingival margin was lining mucosa, '1' when there was a 'partial' presence of KM <2 mm, and '2' when there was a 'complete' presence KM >2 mm)³³⁹.

Radiographic examinations

Peri-apical radiographs were taken in each study as stated above in the follow-up protocol section.

The radiographs were taken with an X-ray digital apparatus supplied with a long cone. Rinn positioning systems were used to ensure reproducibility of the measurement of the MBL³⁰⁷.

The MBL was measured at the mesial and distal sites and was defined as the distance between the implant-abutment connection (machined beveled surface), reference point, and the level of the interproximal first visible bone-to-implant contact, approximated to the nearest 0.01 mm. The known implant diameter was used to calibrate the measurements for any distortions (screen resolution was 1920 x 1200 pixels). If the implant-abutment margin was below the margin of the crestal bone, then it was considered subcrestal and it was given the value of '0'.

The MBL change was defined as the difference between the measured MBL at IP, at BL, at 6 months and 1-year in **Study II**.

The MBL change was defined as the difference between the measured MBL at BL, 1-year, and 3-year in **Study III**.

The MBL change was defined as the difference between the measured MBL at BL and 2-year in **Study IV**.

The radiographic images in **Study II** and **III** were analysed with Illustrator software (Illustrator® CS, Adobe Systems, Inc. San Jose,

CA, USA) on a 24-inch LCD screen (iMacApple Inc, Cupertino, CA) at the Department of Radiology of Sahlgrenska Academy, Gothenburg University, by experienced radiologists, who were otherwise not involved in the studies.

In **Study IV**, the X-rays were analysed by an independent radiologist not involved in the study. Intra-examiner measure variability was determined by re-examining 10% of all measures randomly selected, and the measurement error was calculated.

In **Study III** and **IV** the length of the distal cantilever was calculated on the peri-apical radiograms as the horizontal distance from the perpendicular axis of the implant to the distal portion of the framework.

In **Study III**, the presence of an angle (tilting) between the inclination of the distal implant with the occlusal plane was also calculated and if the angle were equal or exceeded 15°, the implant was considered 'tilted'.

Patients' satisfaction

In **Study III** and **IV** patients were asked to fill out questionnaires related to their satisfaction with the rehabilitation.

The questionnaires were delivered to the patients and the patients returned them one week prior to each visit at the pre-treatment evaluation (PT) and after the treatment at each follow-up visit.

In **Study III** the questionnaires used came from a similar study where fifteen patients, edentulous in the maxilla, were rehabilitated with implant-supported FCD³⁶⁷.

The five addressed questions were:

- 1) Are you satisfied regarding the ability to chew/bite?
- 2) Are you satisfied regarding the ability to speak?
- 3) Are you satisfied regarding the aesthetic of your treatment?
- 4) Are you satisfied regarding the comfort and not having pain eating any food?
- 5) How would you describe your overall satisfaction level?

Five factors were rated on a 1 to 5 scale (Very satisfied=1; Satisfied = 2; Neutral = 3; Dissatisfied = 4; Very dissatisfied = 5). The sum of the five sub-scores was then calculated, ranging from 5 to 25 (best score = 5, worst = 25). Low score range indicated high patient satisfaction.

In **Study IV** a standard version, translated into Italian language, of the OHIP-14 questionnaire was used (Table 9).

OHIP-14 is divided into seven areas of investigation according to the type of question: Q1-Q2 (functional limitation); Q3-Q4 (physical pain); Q5-Q6 (psychological discomfort); Q7-Q8 (physical disability); Q9-Q10 (psychological disability); Q11-Q12 (social disability); Q13-Q14 (handicap). Fourteen items were rated on a 0-4 scale (Never = 0; Hardly ever = 1; Occasionally = 2; Fairly often = 3; Always = 4).

In each patient, the OHRQoL was defined by estimating the OHIP-14 summary score, that is the sum of the 14 sub-scores (possible score range for patient satisfaction: 0 to 56) (best score = 0, worst = 56). High OHIP-14 scores indicate poor OHRQoL, whereas low OHIP-14 scores indicate satisfactory OHRQoL.

Table 9. Oral Health Impact Profile 14 (OHIP-14) questionnaire.
(Study IV)

	Never	Hardly ever	Occa- sionally	Fairly often	Always
A) <u>Functional Limitation</u>					
1) Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures?					
2) Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?					
B) <u>Physical pain</u>					
3) Have you had painful aching in your mouth?					
4) Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?					
C) <u>Psychological discomfort</u>					
5) Have you been self-conscious because of your teeth, mouth or dentures?					
6) Have you felt tense because of problems with your teeth, mouth or dentures?					
D) <u>Physical disability</u>					
7) Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures?					
8) Have you had to interrupt meals because of problems with your teeth, mouth or dentures?					
E) <u>Psychological disability</u>					
9) Have you found it difficult to relax because of problems with your teeth, mouth or dentures?					
10) Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?					

(Table 9 continues on next page)

(Table 9 cont.)

	Never	Hardly ever	Occa- sionally	Fairly often	Always
<u>F) Social disability</u>					
11) Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?					
12) Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?					
<u>D) Handicap</u>					
13) Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?					
14) Have you been totally unable to function because of problems with your teeth, mouth or dentures?					

Clinicians' satisfaction

In **Study III** clinicians were asked to complete a questionnaire on their satisfaction before and after the treatment.

The questionnaire consisted of four questions:

- 1) Are you satisfied regarding our patient's ability to chew/bite?
- 2) Are you satisfied regarding your patient's ability to speak clearly?
- 3) Are you satisfied regarding the aesthetic of your patient?
- 4) How would you describe your overall satisfaction level?

Five factors were rated on a 1 to 5 scale (Very satisfied=1; Satisfied = 2; Neutral = 3; Dissatisfied = 4; Very dissatisfied = 5). The sum of the five sub-scores was then calculated, ranging from 4 to 20 (best score = 4, worst = 20). Low range of score indicated high satisfaction from the clinician.

In **Study IV** clinicians were asked, prior to the final prostheses' delivery, to complete a satisfaction questionnaire.

Five questions were reported on:

- 1) Were the milled bars delivered on time?
- 2) Were the milled bars easy to build up for the final prostheses?
- 3) Did the milled bars fit well with the implants?

- 4) Were the milled bars easy to disassemble?
- 5) Did the milled bars meet your expectations?

Five factors were rated on a 0 -4 scale (Very satisfied = 0; Satisfied = 1; Neutral = 2; Dissatisfied = 3; Very dissatisfied = 4). The sum of the five sub-scores for the prosthodontist was then calculated, ranging from 0 to 20 (best score = 0, worst = 20). Low scores indicate high satisfaction, suggesting how well the implant features declared by the manufacturer met the prosthodontist's expectations.

Complications

The complications were categorised, according to Berglundh et al.¹², into two: Technical and Biological.

Technical complications affected the prostheses as a unit and consisted of chippings and/or fractures of the veneering material (**Study II, III, and IV**), loss of retention of the prostheses (**Study II, III, and IV**), framework fracture (**Study II, III, and IV**), presence of plaque on the prostheses (**Study III**), and abutment-framework connection gaps (**Study III**).

Technical complications that affected the implant and its components were bridge and abutment screw mobility or fractures, and implant fractures.

The biological complication that affected the prostheses was soft tissue inflammation in the edentulous area (**Study III**).

Biological complications included oedema, fistula, hyperplasia, mucositis or peri-implantitis in the treated areas. Mucositis was defined as BoP score >1 in **Study II and III**. On the other hand, in **Study IV**, mucositis was defined as abundant bleeding, different from the dichotomous variable, without any other signs of loss of supporting bone. Peri-implantitis was defined as the presence of an inflammatory lesion in the peri-implant mucosa associated with profuse bleeding on probing, and suppuration and radiographic bone loss around implants²⁷⁸.

The complications were reported and used to calculate the prognostic indexes.

Statistical analysis

In all the three clinical studies, the implant was used as a statistical unit. Continuous variables were presented as the number of observations, mean and standard deviation, minimum, median, maximum, lower, and higher quartile. Discrete variables were presented by frequency and percentage. A histogram with the frequency distribution was generated for visualising and assessing the distribution. The normality of outcome variable distributions was tested with the Kolmogorov-Smirnov test and Shapiro-Wilk test, and the Levene's test was used to evaluate homoscedasticity. For non-normally distributed data, a non-parametric statistical approach was used. The analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS Inc., Chicago, Illinois) and version 22 for Mac (IBM SPSS Statistics for Mac, v.22). Statistical significance was considered as $P < 0.05$.

In **Study II**, differences in MBL change and prosthetic and clinical complications (implant failure, fracture of prosthetic components, bacterial plaque accumulation, BoP, and PPD) were compared between the AL and IL groups. Student's t-test or Mann-Whitney test was used to assess the difference between groups for continuous variables, depending on the normality. Pearson's chi-squared or Fisher's exact test was used in the analysis of contingency tables of categorical data. Survival analyses were performed.

In **Study III**, the RCT was performed following a non-inferiority study design. It was assumed that a maxillary FCD with 4 implants was not inferior to a maxillary FCD with 6-I. MBL change was chosen as the primary endpoint for the analysis of statistical power.

According to studies with similar patient selections, when 6 or more implants were used to support a maxillary FCD, the mean bone loss after 1 year of function ranged between 0.22 and 0.60 mm^{315,388}. Therefore, the 4-implant (4-I) group was not considered inferior to the 6-implant (6-I) group in supporting a maxillary FCD, if the mean difference in MBL change between groups after 1 year was not higher than 0.4 mm (SD 0.80; $H_0: \mu=0.4$ mm; $H_1 > \mu=0.4$ mm).

The sample size, to give a power of 80%, an effect size (d) of 0.5, and an α -error of ≤ 0.05 (two-sided), was calculated as 24 patients in each group. Five patients per group were further included to account

for possible withdrawals from the study, resulting in a target study population of 58 patients.

Patient characteristics, framework specification, prosthetic complication, and status of the opposite dentition were recorded per patient. Implant and surgical characteristics, soft tissue indexes, MBL change, survival, and complication rates were reported per implant.

Given that implants were clustered into subjects, data cannot be assumed as independent. Accordingly, a generalized linear mixed model was applied to evaluate differences between groups on the dependent variables (MBL change, PI, Bop, PPD). In detail, the group variable (4I and 6I) was included as the fixed effect and patients were included as the random effect. A further linear mixed model was conducted including the loss of KM between BL-1Y and BL-3Y as a categorical predictor (absence, partial or complete) on the influence of MBL change, PI, Bop, PPD over time. The statistical analyses were performed using the software package SPSS (IBM Corporation, Armonk, USA). Binary variables were evaluated using Fisher's exact test.

In **Study IV**, Wilcoxon rank-sum test was used to compare the parameters related to MBL and clinical parameters between baseline and follow-up.

The hypothesis that the length of the cantilever could influence the MBL change in distal implants was evaluated by comparing the difference between MBL changes in mesial and distal implants, using the Wilcoxon rank-sum test. The null hypothesis was that 'there is no difference in MBL change around mesial and distal implants supporting the prosthetic reconstruction'.

The OHIP scores before and after treatment were evaluated using a repeated measure analysis of variance (ANOVA). Multiple regression models were used to evaluate whether patient baseline characteristics (age, sex, smoking, diabetes) influenced the pre-/post-treatment OHIP scores.

RESULTS

Mechanical Fatigue Test (Study I)

When a framework was seated into the experimental model and before the fixation with the torquing procedures, a misfit was clearly visible (Figure 17). The misfit was present in both misfit groups, and was also detectable on radiographic images after the final torque fixation (Figure 18).

Figure 17. Image shows that prior to torquing the framework to the implant, a misfit was clearly visible. **(Misfit groups Study I)**

Figure 18. X-rays image that reveal a detectable misfit after final torque Red arrow indicates a gap between framework and implant. **(Misfit groups Study I)**

None of the mechanical components presented distortion or fracture at the macroscopic level during the fatigue test. After the test, no microfractures of the prosthetic screws were detected.

The microscopy evaluation demonstrated visible scratches visible in the inner part of the conical portion of the implants regardless of the groups. SEM and CT- 3D analysis revealed one implant out of eight from the misfit/no bone loss group with a microfracture in the inner part of the conical interface (Figures 19 - 20). The SEM analysis revealed scratches, wear, minor damages, and titanium debris on the interface of the majority of the implants regardless of group.

Figure 19. SEM (Hitachi TM3000, Hitachi) analysis revealed one implant from Test group - Position A with a micro-fracture in the inner part of the conical interface. **(Study I)**

Figure 20. CT- 3D analysis (ZEISS Stemi 2000-C Stereo Microscope) revealed one implant out of eight from the misfit/no bone loss group with a microfracture in the inner part of the conical interface. **(Study I)**

Finite Element Analysis (Study I)

Decreasing the mesh did not significantly affect the von Mises stress level of the circumferential opening of the coronal portion of the implant (Figure 21).

Figure 21. Von Mises stress level at the circumferential opening, starting from the misfit contact side, at the coronal portion of the implant of three different mesh sizes. (Study I)

Therefore, to reduce simulation time, a mesh size of 0.075 mm in the implant-framework interface was used for all other simulations. Effective stress lower than 375 MPa represents a lifetime ($N > 1 \times 10^6$ cycles) (Figure 9) and the green represents the fatigue limit of titanium at 1×10^6 cycles. The simulated effective stress levels in the coronal body were higher in the misfit groups compared with the groups with no-misfit. The misfit groups presented effective stress levels, above 375 MPa, that penetrated the entire wall thickness, and the implants without bone loss presented an effective stress level above 375 MPa along its axial direction (Figure 22). In the no-misfit group, the area presenting effective stress levels above 375 MPa in the conical connection was larger for the bone loss group compared with the no bone loss group (Figure 23).

Figure 22. Simulated effective stress levels in misfit groups.
(A) Misfit group, 0 mm bone loss, external side.
(B) Misfit group, 0 mm bone loss, internal side.
(C) Misfit group, 3 mm bone loss, external side.
(D) Misfit group, 3 mm bone loss, internal side. **(Study I)**

Figure 23. Simulated effective stress levels in no-misfit groups.

(A) Misfit group, 0 mm bone loss, external side.

(B) Misfit group, 0 mm bone loss, internal side.

(C) Misfit group, 3 mm bone loss, external side.

(D) Misfit group, 3 mm bone loss, internal side. **(Study I)**

Clinical Studies (Study II-III-IV)

All implants were osseointegrated in **Study II** and **IV** (survival rate 100%) and clinically stable while in **Study III** one implants was lost during the second surgery in the 6-I group with a survival rate of 99.6%

In **study III** three drop-outs, all in the 6-I group, were registered before the completion of the three-year follow-up (Figure 11) and therefore, their implants were not included in the statistical analyses at the 3Y.

Demographics according to first-stage surgical procedure

In **Study II**, ITV resulted in a mean of 26.5 Ncm (SD 10.2; 9-58) and its specifications according to jaws, bone quality and drilling protocol are shown in Table 10.

Table 10. Results for ITV in jaws, bone quality and drilling protocol.

Note: ITV is expressed in N/cm; N. (number of implants); SD (standard deviation) Min (Minimum); Max: (Maximum). (**Study II**)

Jaw	N	ITV	pValue
		Mean (SD;Min-Max)	
Mandible	66	31.7 (9.8;12-58)	<.001
Maxilla	53	20.1 (6.6; 9-33)	
Bone Quality (L&Z)			<.001
1	6	50.7 (4.2;47-58)	
2	49	32.0 (6.4;21-48)	
3	47	22.3 (5.9;11-33)	
4	17	13.9 (3.8;9-25)	
Drilling protocol			<.001
S	31	21.2 (7.9;10-48)	
S-A	17	20.3 (6.0;10-32)	
S-B	18	29.3 (9.5;9-45)	
S-X-B	53	30.7 (10.6;11-58)	
Total	119	26.5 (10.2;9-58)	

There was a moderate correlation between the last drill used at the implant surgery installation and the bone quality of the implant site ($R = -0.638$, $R^2 = 0.407$, $P < 0.001$; Spearman correlation).

In **Study III**, of the 112 posteriorly placed implants in both groups, 64 were positioned tilted (57.1%). In the 4-I group reported 45 (80.4%) out of 56 posterior implants tilted with a mean angulation of 26.27° (SD 7.97; min 15°- max 45°) while in the 6-I group, 19 (33.9%) out of 56 posterior implants were tilted with a mean angulation of 22.11° (SD 5.11; min 15°-max 30°) (Table 11).

Table 11. Angulation of the tilted implants in each group.

Note: 4-I (four-implant group); 6-I (six-implant group); N. (number of tilted implants); Values are expressed in degree. **(Study III)**

	N.	Mean	SD	Min	Max
Group					
4-I	45	26.27°	7.97°	15°	45°
6-I	19	22.11°	5.11°	15°	30°
Total	64	25.03°	7.45°	15°	45°

Frameworks

In **Study III**, the cantilever had a mean length of 11.79 mm (SD 4.60; min 2.18 mm - max 21.43 mm) in the 4-I group and a mean length of 8.47 mm (SD 4.57; min 0.0 mm - max 18.48 mm) in the 6-I group (Table 12).

In **Study IV**, the mean cantilever length of the mesostructured was as follows: on the left side 8.39 ± 2.97 mm (range 0.00 to 13.66 mm); on the right side 8.57 ± 3.11 mm (range 0.00 to 13.94 mm). The mean cantilever length of the suprastructure was as follows: on the left side 10.22 ± 6.07 mm (range 0.00 to 19.60 mm); on the right side 10.44 ± 6.35 mm (range 0.00 to 22.08 mm) (Figures 15 - 29).

Table 12. Cantilever length (mm) in each group. **(Study III)**

	N.	Mean	SD	Min	Max
Group					
4-I Left	28	12.02	4.34	2.23	20.10
4-I Right	28	11.56	5.69	0.00	24.29
4-I Total	28	11.79	4.60	2.18	21.43
6-I Left	28	8.59	4.91	0.00	18.48
6-I Right	28	8.36	4.93	0.00	17.24
6-I Total	28	8.47	4.57	0.00	18.48

Clinical Findings **Study II**

Plaque index

Plaque scored 1 in 0.4% of 476 of sites at BL (2 sites); 9.9% at 6 months (47 sites); 13.9% at 1-year (66 sites). No PI scores of 2 or 3 were registered and no statistically significant difference was observed between the two timepoints.

Bleeding on Probing

BoP in the total implants pooled together was present at BL in 242 (50.8%) out of 476 sites. At 6 months and at 1-year BoP was registered in 271 (56.9%) and in 227 (47.7%) out of 476 sites respectively. The difference between the two groups was statistically significant. The presence of BoP increased with time in the IL group while it decreased in the AL group. The main changes occurred between BL and 6 months in the IL sites, and between 6 months and 1 year in the AL sites (Table 13).

Of the 476 sites, 66 presented plaque, and 227 presented BoP, and 54 presented concomitant plaque and BoP at 1 year. This means that 81.8% (54/66) of the sites with plaque had BoP, but only 23.8% of the sites with BoP had plaque. The correlation between BoP and plaque was weak ($R = 0.274$, $R^2 = 0.075$, $P < 0.001$; Spearman correlation).

Probing Pocket Depth

The mean PPD at BL, 6 months and 1-year, and the difference between the two groups are reported in Table 14. There was a statistically significant difference between PPD of the IL and AL groups for all the sites, at all follow-up time points. Moreover, the PPD significantly decreased with time in the AL group, but not in the IL group.

Keratinised Mucosa

Only the molar sites presented a statistically significant difference between the widths of the buccal KM of the two groups. The correlation between the width of keratinised mucosa and MBL at 1 year was very weak ($R = -0.038$, $R^2 = 0.001$, $P = 0.700$; Pearson correlation). There was a general likelihood of a decrease in buccal KM with time (Table 15).

Table 13. Bleeding on probing (BoP) between the two groups.

Note: BL (base line); 6M (6 months); 1Y (1-year); IL (implant level); AL (abutment level).

Percentage of sites (yes/total). (**Study II**)

	IL	AL	
BL	44.4% (103/232)	57.0% (139/244)	0.006**
6M	56.9% (132/232)	57.0% (139/244)	
1Y	57.3% (133/232)	38.5% (94/244)	<.001***
BL - 6M	<0.007**		
6M - 1Y		<.001***	
BL - 1Y	<0.005**	<.001***	

Table 14. Probing pocket depth (PPD)(mm) between the two groups.

Note: BL (base line); 6M (6 months); 1Y (1-year); IL (implant level); AL (abutment level).

Mean PPD (mm)±SD (min-max)(numebr of sites). (**Study II**)

	IL	AL	
BL	3.49±0.83 (2-6) (n=232)	2.97±1.06 (1-6) (n=244)	<.001***
6M	3.37±0.85 (2-6) (n=220)	2.88±1.18 (0-8) (n=236)	<.001***
1Y	3.46±1.07 (1-7) (n=216)	2.59±1.09 (1-7) (n=224)	<.001***
BL - 6M			
6M - 1Y		<.001***	
BL - 1Y		<.001***	

Table 15. Comparison of the width of the buccal keratinised mucosa (KM) between the two groups.

Note: BL (base line); 6M (6 months); 1Y (1-year). IL (implant level) AL (abutment level). Mean KM(mm) $\pm$ SD (min-max)(number of sites). **(Study II)**

	IL	AL	
	BL		
Incisive	-	2.00 $\pm$ 0.00 (2-2) (n=5)	
Canine	2.00 $\pm$ 0.00 (2-2) (n=3)	2.00 $\pm$ 0.00 (2-2) (n=2)	
Premolar	1.96 $\pm$ 0.209 (1-2) (n=23)	1.87 $\pm$ 0.344 (1-2) (n=23)	
Molar	1.81 $\pm$ 0.397 (1-2) (n=32)	1.71 $\pm$ 0.461 (1-2) (n=31)	
	6M		
Incisive	-	2.00 $\pm$ 0.00 (2-2) (n=5)	
Canine	2.00 $\pm$ 0.00 (2-2) (n=2)	2.00 $\pm$ 0.00 (2-2) (n=2)	
Premolar	1.95 $\pm$ 0.213 (1-2) (n=22)	1.62 $\pm$ 0.740 (0-2) (n=21)	
Molar	1.94 $\pm$ 0.250 (1-2) (n=31)	1.48 $\pm$ 0.677 (0-2) (n=31)	0.001 **
	1Y		
Incisive	-	2.00 $\pm$ 0.00 (2-2) (n=4)	
Canine	2.00 $\pm$ 0.00 (2-2) (n=2)	2.00 $\pm$ 0.00 (2-2) (n=2)	
Premolar	1.85 $\pm$ 0.366 (1-2) (n=20)	1.45 $\pm$ 0.759 (0-2) (n=20)	
Molar	1.86 $\pm$ 0.351 (1-2) (n=29)	1.43 $\pm$ 0.626 (0-2) (n=30)	0.003 **

Clinical Findings **Study III**

The clustering effects of patients were significant for all the soft tissue indexes.

Considering this, the analysis reported no significant differences between the groups for PI, BoP and PPD at each time point as well as in between the visits (Tables 16 – 17 - 18).

The presence of KM during each visit is reported in Table 19 and in Figure 23.

It was also investigated whether sites with loss of KM between BL-1Y and BL-3Y had an influence on the MBL change, PI, BoP and PPD. Results showed that sites with a diminishing with of KM presented no significant differences in MBL change ($F(2, 253.750) = 0.002, = .998$) in BoP ($F(2, 253.682) = 0.156, p = .856$) and in the PI change ($F(2, 246.077) = 2.709, = .069$). The effect of a diminishing KM value presented a significant influence on the PPD ($F(2, 256.864) = 4.743, p = .009$).

Table 16. Plaque Index (PI) for all the implants in the two groups and the difference between them.

Note: *n* (number of implants); values are expressed in percentage (%). (**Study III**)

	4-Implants			6-Implants			<i>F</i> -value (a)	<i>P</i> -value (a)
	<i>n</i>	Mean±SD	95% CI	<i>n</i>	Mean±SD	95% CI		
BL	112	1.12±6.18	[-0.04/2.27]	167	3.74±18.74	[0.88/6.61]	0.509	.479
1Y	112	15.63±25.58	[10.83/20.42]	167	30.69±37.29	[24.99/36.39]	3.662	.061
3Y	112	20.54±27.92	[15.31/25.76]	149	31.54±35.76	[25.75/37.33]	2.245	.140
BL-1Y	112	-14.51±25.48	[-19.28/-9.74]	167	-26.95±35.35	[-32.35/-21.54]	2.722	.105
BL-3Y	112	-19.42±28.02	[-24.67/-14.17]	149	-31.38±35.97	[-37.20/-25.55]	2.635	.111
1Y-3Y	112	-4.91±32.33	[-10.96/1.14]	149	-2.35±34.18	[-7.88/3.18]	0.128	.722

Table 17. Bleeding on probing (BoP) for all the implants in the two groups and the difference between them.

Note: *n* (number of implants); values are expressed in percentage (%). **(Study III)**

	4-Implants			6-Implants			F-value (a)	P-value (a)
	<i>n</i>	Mean±SD	95% CI	<i>n</i>	Mean±SD	95% CI		
BL	112	41.07±40.67	(33.46/48.69)	167	29.64±36.47	(24.07/35.21)	1.755	.191
1Y	112	51.12±36.20	(44.34/57.89)	167	48.65±37.05	(42.99/54.31)	0.128	.722
3Y	112	45.98±33.48	(39.71/52.25)	149	46.81±38.37	(40.60/53.02)	0.013	.911
BL-1Y	112	-10.05±45.58	(-18.58/-1.51)	167	-19.01±40.54	(-25.21/-12.82)	1.034	.314
BL-3Y	112	-4.91±48.61	(-14.01/4.19)	149	-14.60±39.75	(-21.03/-8.16)	1.117	.296
1Y-3Y	112	5.13±37.24	(-1.84/12.10)	149	-1.01±40.05	(-7.49/5.48)	0.722	.399

Table 18. Probing pocket depth (PPD)(mm) for all the implants in the two groups at each visit and difference between visits.

Note: *n* (number of implants). **(Study III)**

	4-Implants			6-Implants			Group difference	
	<i>n</i>	Mean±SD	95% CI	<i>n</i>	Mean±SD	95% CI	F-value (a)	P-value (a)
BL	112	3.28±0.89	(3.12/3.45)	167	2.91±1.12	(2.74/3.08)	3.472	.068
1Y	112	3.06±0.74	(2.92/3.20)	167	2.90±1.17	(2.72/3.08)	0.646	.425
3Y	112	3.07±0.78	(2.92/3.21)	149	2.80±1.07	(2.62/2.97)	1.855	.179
BL-1Y	112	0.22±0.67	(0.10/0.35)	167	0.01±0.51	(-0.07/0.09)	3.988	.051
BL-3Y	112	0.22±0.69	(0.09/0.35)	149	0.11±0.72	(-0.01/0.22)	0.651	.424
1Y-3Y	112	-0.01±0.58	(-0.11/0.10)	149	0.07±0.63	(-0.03/0.17)	0.383	.539

Table 19. Presence of Keratinised mucosa (KM) at different visits at the buccal side of each implant in both groups over time. (Study III)

KM	Baseline			1Y			3Y					
	N	Absent %	Partial %	Complete %	N	Absent %	Partial %	Complete %	N	Absent %	Partial %	Complete %
Group												
4-l group	112	0	8.0	92.0	112	0	15.2	84.8	112	9.8	17.0	73.2
6-l group	167	0	19.8	80.2	167	0.6	22.8	76.6	149	12.8	20.8	66.4
Total	279	0	15.1	84.9	279	0.4	19.7	79.9	261	11.5	19.2	69.3

Figure 24. Keratinised mucosa at the buccal side in both groups. (Study III)
 Note: 4-I (four implants); 6-I (six implants); BL (baseline); 1Y (1-year); 3Y (3-year).

Clinical Findings **Study IV**

Plaque index

Plaque was present on the surfaces of 34 site out 740 (4.6%) at BL and 55 sites out of 740 (7.4%) at FU. No statistically significant difference was observed between the two timepoints.

Bleeding on Probing

BoP was present on the surfaces of 114 sites out of 740 (15.41%) at BL and 165 sites out of 740 (22.30%) at FU. A statistically significant difference ($P = 0.032$) was present between BL and FU.

Probing pocket depth

The mean PPD at baseline for all implants averaging all sites was 2.46 ± 1.01 mm (range 0.00 to 6.00 mm). At a 2-year follow-up mean PPD for all implants, averaging all sites, was 2.46 ± 0.94 (range 0.00 to 6.00 mm). No statistically significant difference was observed between the two time points.

Radiographic examinations

In **Study II**, the difference between the MBL changes of the IL and AL groups was statistically significant at 6 months and 1 year compared to baseline. The MBL and the MBL changes are reported in Tables 20 - 21, respectively. There was no difference in MBL change, between smokers and non-smokers or between implants of different diameter Figure 25.

Figure 25. X-rays at each time point in abutment level patient (AL) and in implant level patient (IL). Implant Placement (IP); Prostheses Delivery, Base line (BL); six months follow-up (6M); one year follow up (1Y). (**Study II**)

Table 20. MBL (mm) between the groups at different visits.

Note: IP (implant placement); BL (base line); 6M (6 months); 1Y (1-year); n (number of implants); SD (standard deviation). (**Study II**)

	IL		AL	
	n	Mean $\pm$ SD	n	Mean $\pm$ SD
IP	57	0.000 $\pm$ 0.000	61	-0.011 $\pm$ 0.065
BL	58	-0.146 $\pm$ 0.310	61	-0.112 $\pm$ 0.238
6 M	51	-0.263 $\pm$ 0.293	59	-0.134 $\pm$ 0.296
1Y	58	-0.231 $\pm$ 0.264	61	-0.117 $\pm$ 0.308

Table 21. MBL change (mm) between the groups at different time.

Note: IP (implant placement); BL (base line); 6M (6 months); 1Y (1-year); n (number of implants); SD (standard deviation). (**Study II**)

		IL	AL	<i>P value *</i>
		n	n	
IP - BL	n	57	60	
	Mean $\pm$ SD	-0.148 $\pm$ 0.312	-0.103 $\pm$ 0.234	
	95% CI	-0.231 to -0.065	-0.163 to -0.042	
BL – 6M	n	51	59	.002**
	Mean $\pm$ SD	-0.106 $\pm$ 0.334	-0.018 $\pm$ 0.214	
	95% CI	-0.200 to -0.011	-0.074 to 0.037	
BL – 1Y	n	58	61	.003**
	Mean $\pm$ SD	-0.086 $\pm$ 0.313	-0.005 $\pm$ 0.222	
	95% CI	-0.168 to -0.004	-0.062 to -0.052	

In **Study III**, there was no significant differences between the two groups in MBL change, between BL-1Y, between BL-3Y and between 1Y-3Y (Table 22).

The MBL, in the 4-I group was 0.30 $\pm$ 0.50 mm at BL, 0.24 $\pm$ 0.31 mm at 1Y and 0.24 $\pm$ 0.38 mm 3Y. In the 6-I group, MBL was 0.14 $\pm$ 0.32 mm at BL, 0.16 $\pm$ 0.35 mm at 1Y and 0.12 $\pm$ 0.26 mm at 3Y. There was a statistically significance difference between the groups at BL and 3Y.

The mean MBL change of straight and tilted implants was evaluated in all patients, and the difference was compared to assess if tilted

implants had lost more bone. However, no statistically significant difference was observed in the MBL change of straight vs. tilted implants. The mean MBL change was evaluated based on the height of the abutments used, and no statistically significant difference was present among the groups.

The Frequency distribution of the MBL at all the implants are reported in Table 23.

Table 22. Marginal bone level (MBL) (mm) mean±SD (95% Confidence interval)(Minimum-Maximum) for all the implants in the two groups at each visit and the MBL change (mm) mean±SD (95% Confidence interval)(Minimum-Maximum) between visits.

Note: *n*: number of implants; (a) Linear Mixed Model; Negative values represent Bone Loss. (Study III)

	4-Implants				6-Implants				Group difference	
	<i>n</i>	Mean±SD	95% CI	min-max	<i>n</i>	Mean±SE	95% CI	min-max	<i>F</i> -value (a)	<i>P</i> -value (a)
BL	112	0.30±0.50	(0.21/0.40)	(0.00/2.34)	167	0.14±0.32	(0.09/0.18)	(0.00/1.949)	4.222	.045*
1Y	112	0.24±0.31	(0.18/0.29)	(0.00/1.14)	167	0.16±0.35	(0.11/0.22)	(0.00/2.20)	1.352	.250
3Y	112	0.24±0.38	(0.17/0.31)	(0.00/2.60)	149	0.12±0.26	(0.08/0.17)	(0.00/1.41)	4.933	.031*
BL-1Y	112	0.07±0.36	(0.00/0.14)	(-0.58/1.57)	167	-0.03±0.28	(-0.07/0.02)	(-2.20/1.14)	2.830	.099
BL-3Y	112	0.06±0.45	(-0.02/0.14)	(-1.72/1.46)	149	0.01±0.30	(-0.04/0.06)	(-1.41/1.94)	0.527	.472
1Y-3Y	112	-0.01±0.27	(-0.06/0.04)	(-1.67/0.76)	149	0.01±0.18	(-0.02/0.04)	(-0.88/0.80)	0.511	.478

Table 23. Numbers and percentage of implants dived in 6 groups according to the Marginal Bone Level (MBL) in each visit for all the implants pooled together and divided in each group. **(Study III)**

	0 mm		0.01mm/0.5mm		-0.51mm/-1.00mm		-1.01mm/-1.50mm		-1.51mm/-2.00mm		>-2.00mm		Total
Total	N. Implants		N. Implants		N. Implants		N. Implants		N. Implants		N. Implants		N. Implants
BL	191	68.5%	48	17.2%	24	8.6%	9	3.2%	5	1.8%	2	0.7%	279
1Y	179	64.2%	57	20.4%	35	12.5%	5	1.8%	2	0.7%	1	0.4%	279
3Y	173	66.3%	56	21.5%	26	10.0%	5	1.9%	0	0.0%	1	0.4%	261
4-Implant													
Group													
BL	62	55.4%	28	25.0%	12	10.7%	5	4.5%	3	2.7%	2	1.8%	112
1Y	61	54.5%	28	25.0%	21	18.8%	2	1.8%	0	0.0%	0	0.0%	112
3Y	64	57.1%	27	24.1%	19	17.0%	1	0.9%	0	0.0%	1	0.9%	112
6-Implant													
Group													
BL	129	77.2%	20	12.0%	12	7.2%	4	2.4%	2	1.2%	0	0.0%	167
1Y	118	70.7%	29	17.4%	14	8.4%	3	1.8%	2	1.2%	1	0.6%	167
3Y	109	73.2%	29	19.5%	7	4.7%	4	2.7%	0	0.0%	0	0.0%	149

The cumulative frequency distribution of the MBL change between BL and 1-year and between BL and 3-year at implant and subject level for are reported in Figures 26 - 27.

Figure 26. Cumulative frequency distribution at all implants pooled together between BL-1Y and BL-3Y. (Study III)

Figure 27. Cumulative frequency distribution at all subjects pooled together between BL-1Y and BL-3Y. (Study III)

An MBL equal to 0 in all the implants per subject (meaning subjects whose implants had bone located at the reference point) was reported in 20 patients (35.7%) at BL, 16 patients (28.6%) at 1 year and 11 patients (20.8%) at 3 years. The frequency in both groups are reported in Figure 28.

Figure 28. Frequency (%) of subjects with a MBL equal to 0 in all the implants (meaning subjects whose implants had bone located at the reference point) at each visit all plots and in each group (BL, 1Y, 3Y). (Study III)

In **Study IV**, the mean MBL changes between BL and 2-year were associated with a crestal bone gain of 0.02 ± 0.21 mm (median 0.21 mm; min. -0.49 mm; max. to 1.19 mm). No statistically significant difference ($P > 0.05$) was observed between BL and 2-year (Figure

29). A statistically significant difference was found in MBL, of TX and EV implants, at each visit, as for the MBL changes between BL and 2-year (Table 24).

The length of cantilever did not have any statistical impact on the MBL change of posterior implants.

Table 24. Marginal bone level (MBL mm) at baseline (BL) and 2-year and MBL change between the 2 time points (BL-2-year).

Note: P-value: Wilcoxon rank-sum; Negative values represent Bone Loss. **(Study IV)**

		BL	2-year	BL-2-year
Total	Min.	0,00	0,00	1,19
	Max.	-1,78	-1,46	-0,49
	Mean	-0,30	-0,27	0,02
	Median	-0,14	-0,15	0,00
	SD	0,40	0,35	0,22
Type of implant				
OsseoSpeed TX	Min.	0,00	0,00	1,19
	Max.	-1,78	-1,46	-0,49
	Mean	-0,37	-0,32	0,05
	Median	-0,21	-0,18	0,00
	SD	0.45	0.40	0.25
OsseoSpeed EV	Min.	0,00	0,00	0,25
	Max.	-0,80	-0,81	-0,49
	Mean	-0,14	-0,17	-0,03
	Median	0,00	-0,11	0,00
	SD	0,18	0,21	0,11
		0.000***	0.009**	0.022*

Patients satisfaction

In **Study III**, the mean patient satisfaction score at Pre-Treatment (PT) had corresponding sum of scores of related questions of 17.40 ± 2.78 (min 13 – max 25). At BL the score was 7.25 ± 2.03 (min 5 – max 14). The scores were 7.40 ± 2.26 (min 5 – max 13) at 1 year and 7.81 ± 2.40 (min 5 – max 14) at 3 years (Figure 30).

Figure 29. X-rays at the prostheses delivery visit, base line, (A) and at the 2-year. (Study IV)

Figure 30. Summary of the patient's score before treatment (PT), and at BL, 1Y and 3Y. (Study IV)

Figure 31. Box-and-whisker plots of OHRQoL factors for the questionnaire dispensed (A) pre-treatment and at (B) 1-month, (C) 3-month, (D) 2-year. In the box-and-whisker plot, the central box represents the values from the lower to upper quartile (25th–75th percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding ‘outside’ and ‘far out’ values, which are displayed as separate points. **(Study IV)**

In **Study IV**, the median satisfaction scores for the 14 OHRQoL items assessed at PT, 1 month, 3 months and 2 years post-treatment are summarised in Figure 31. For all questions, the scores decreased significantly post-treatment as compared to pre-treatment ($P < 0.0001$).

The mean pre-treatment OHIP-14 score was 22.88 ± 9.4 (range 1 to 44). After 1 month, 3 months and 2 years of treatment, the mean score was 2.25 ± 3.3 (range 0 to 18), 2.35 ± 3.9 (range 0 to 21) and 2.40 ± 3.9 (range 0 to 22), respectively (Figure 32). At each follow-up, the scores were significantly different from the pre-treatment ($P < 0.0001$), while they were not significantly different from 1 month, 3 months and 2 years ($P > 0.05$).

Figure 32. Pre-treatment and post-treatment OHIP-14 score summary 1 month (1M), 3-month (3M) and 2-year (2Y). (**Study IV**)

Multiple regression models were computed to evaluate whether patient characteristics such as age, smoking, gender affected the OHIP-14 summary score pre- and post-treatment, or their difference (namely, the perception of QoL improvement). The results showed that none of the patient's characteristics had a significant influence on OHIP scores or their difference.

Clinicians satisfaction

In **Study III**, the sum of the mean clinician satisfaction scores at PT was 13.36 ± 2.19 (min 10 - max 20). At BL, 1 year and 3 years, the score was 5.64 ± 1.30 (min 4 - max 8), 5.87 ± 1.37 (min 4 - max 10) and 6.68 ± 1.44 (min 4 - max 10), respectively.

In **Study IV**, the prosthodontists were satisfied, on average, about the delivery and the versatility of the two milled bars, this reflected in a mean score of 3.4 ± 4 .

Technical complications affected the prostheses

In **Study II**, one chip-off fracture was reported in the IL group (position 23) and it was resolved by polishing. Thus, the overall failure rate of the screw-retained FPD at a 1-year control/evaluation was 2% (Table 25).

In **Study III**, 12 patients (21.4%) reported complications with the prostheses after 1 year. Six patients (4-I group) presented with fractures of the entire prosthetic tooth. Four patients (6-I group) presented with fractures of two prosthetic teeth each. Two patients (one in the 4-I group and one in the 6-I group) presented with the chipping of a prosthetic tooth.

At 2 years, two further patients (3.6%) (one for each group) were found with complications of the prostheses. The patient in the 4-I group, who also had a complication at 1 year, presented two chippings, one in the same tooth that was observed at 1 year. The patient in the 6-I group presented with a fracture of one prosthetic tooth.

At 3 years, an additional 11 patients had complications (one of them was the second experience). Seven (six in the 4-I group and one in the 6-I group) had one tooth with chipping (one patient) or dentition fracture (six patients). One patient in the 4-I group had two teeth with chippings. One patient in the 6-I group had two teeth with fractures. Two patients (one in each group) had three teeth with fractures (Table 25).

Prosthetic complications affected 23 patients over the 3 years of the study; however, two patients experienced complications twice during the 3 years, thus an adjusted 25 patients experienced complications

at a total rate of 47.2%. In 20 patients (35.7%), the prostheses had to be removed and sent to the lab for adjustment. The prosthesis complications occurred in 16 patients in the 4-I group (28.6% of the patients) and nine in the 6-I group (16%) (Table 25).

These groups of patients presented the following dentition in the mandible: 11 mandible FCD, 4 fixed partial prostheses on implants in the posterior regions and natural dentition in the frontal area, 3 natural dentitions (ND) in the frontal area and removable dentures in the posterior regions, 1 with ND with an implant at position 36, 1 natural dentition in frontal and molar regions and implants in premolar regions, and 3 NDs.

Because of the above-reported prosthetic complications, acrylic night-guards were delivered to seven patients.

Presence of plaque on the prostheses

After removing the FCD, 27 patients (16 in the 4-I group and 11 in the 6-I group) reported plaque on the prostheses at 1 year and 33 patients (21 in the 4-I group and 12 in the 6-I group) at 3 years.

In **Study IV**, one patient reported a technical complication consisting of chipping of the resin in a left mandibular central incisor.

Two patients from different centres reported lost friction between the two bars. The retention elements in the suprastructure were replaced with new ones in the female patient (Table 25).

Table 25. Technical complications affected the prostheses in **Study II-III-IV.**

	Study II		Study III			Study IV	
	1Y		1Y	2Y	3Y	3 Year overall % (N./ Total Prostheses)	2Y
Prostheses							
Chipping of the Veneering material	1		2 §	1 § (same patient at 1Y)	2	9.43% (5/53)	1
Fracture of the Veneering material			10 ¶	1	9 ¶ (same patient at 1Y)	37.74% (20/53)	
% (N./ Total Prostheses)	2% (1/50)		21.43% (12/56)	3.57% (2/56)	20.75% (11/53)	47.17% (25/53)	2.5% (1/40)
Plaque on the prostheses			48.21% (27/56)		62.26% (33/53)		

Table 26. Technical complications affected implants components in **Study II-III-IV.**

	Study II		Study III			Study IV	
	1Y		1Y	2Y	3Y	3 Year overall % (N./Total Implants)	2Y
Technical/Mechanical							
bridge screw loosening			1		1	0.77% (2/261)	2
abutment screw fracture				1	1	0.77% (2/261)	
% (N./Total Implants)			0.36% (1/279)	0.36% (1/279)	0.77% (2/261)	1.53% (4/261)	1.1% (2/185)

Table 27. Biological complications affected the prostheses in **Study II-III-IV.**

	Study III			Study IV
	1Y	2Y	3Y	
				2Y
Soft tissue inflammation in edentulous area	16.07% (9/56)		18.87% (10/53)	

Table 28. Biological complications affected implants in **Study II-III-IV.**

	Study III				Study IV
	1Y	2Y	3Y	3 Year overall % (N./Total Implants)	
Biological					2Y
Edema	2° (two implants in one patient)		1+2° (same patient at 1Y)	1.92% (5/261)	
Fistula	1		1* (same patient at 2Y with perimplantitis)	0.77% (2/261)	
Mucositis	2 (two implants in one patient)		5	2.68% (7/261)	0.54% (1/185)
Perimplantitis		1*		0.38% (1/261)	
% (N./Total Implants)	1.79% (5/279)	0.36% (1/279)	3.45% (9/261)	5.74% (15/261)	0.54% (1/185)

Technical complications affected implants components

In **Study II**, one abutment loosening occurred at BL. The abutment was secured using a torque wrench, before the final FPD delivery (Table 26).

In **Study III**, one patient in the 4-I group presented one bridge screw loosening in one implant at 1 year. At the 2 years follow-up, one patient in the 4-I group presented an abutment screw fracture in one implant. At 3 years, one patient presented one bridge screw fracture in one implant and one patient presented a mobile bridge screw fracture. Both patients were in the 4-I group. Thus, the overall complication rate at 3 years follow-up was 1.53% at implant level and 7.55% (four patients) at the patient level (Table 26).

In **Study IV**, one patient presented two prosthetic screws that had loosened in the mesostructure (Table 26).

Biological complications affected the prostheses

In **Study III**, nine patients (seven in the 4-I group and two in the 6-I group) had inflammation in the edentulous area at 1 year, probably due to compression of the prostheses, and as a consequence, eight prostheses were realigned.

At 3 years, 10 patients (seven in the 4-I group and three in the 6-I group) presented inflammation in the edentulous area, and this had already been observed for six of them at 1 year. All the prostheses of the patients who were followed-up at 3 years were realigned (Table 27).

Biological complications affected the implants

In **Study III** at 1 year, three patients reported complications. One patient in the 6-I group showed oedema around two implants with no bone loss at BL, 1 year, and 3 years. One patient in the 4-I group presented a fistula (no suppuration) (Table 28). The MBL of this implant was 0.28 mm at BL, 0.82 mm at 1 year, and 0.79 mm at 3 years. One patient presented mucositis (BoP 2) around two implants. At 2 years, one patient in the 4-I group presented with peri-implantitis of one implant. The implant showed pus, a BoP score of 3, oedema, and hyperplasia. The MBL of this implant was 0.88 mm at BL, 0.93

mm at 1 year, and 2.60 mm at 3 years. The patient was treated, and the infection resolved (Figure 33).

At 3 years, nine patients reported complications. One patient had oedema around two implants at the 3 years recall (the same patient, and 2 implants, as reported at 1 year in the 6-I group). One patient in the 4-I group showed oedema around one implant. One patient in the 4-I group showed a fistula in one implant. The same patient reported peri-implantitis at 2 years (Figure 33).

The fistula may have resulted from the healing process and persisted. This patient also reported chipping of the prostheses in the same position at 3 years and this was included in the prosthetic complications. Five patients presented with mucositis (BoP 2) around one implant in each of them.

In total, at 3 years, 15 (5.74%) implants in 10 (18.86%) patients were affected by biological complications. The biological complications were treated by the cleansing of the implant sulcus and irrigation with sterile saline

In **Study IV**, only one patient presented with peri-implant mucositis (Table 28).

Figure 33. Patient of the 4-implant group. A) Orthopantomogram at baseline. B) Patient at the 2-year visit presented periimplantitis at implant in position 21. C) Patient at the 3-year visit presented fistula at implant in position 21 (black arrow). D-E-F-G) X-ray at visit Base-Line, 1-year, 2-year and 3-year. **(Study III)**

DISCUSSION

The effects of misfit and supporting bone levels on IL FPDs on the generation of implant cracks. (Study I)

In **Study I** the effect of a precise misfit condition was evaluated when a milled Ti bar was screw-retained at implant-level in two ICC implants, simulating an FPD.

The investigation was performed *in vitro*, with a mechanical test and a simulation model, to detect and predict the fatigue and force of displacement. The mechanical model was developed with a cycling load test so that the ICC implants were subjected to repetitive stresses until they failed under fatigue. The calculation model was built according to the fatigue theories, where repetitive applied force below yield, generates stress that would result in material failure with time.

In screw-retained partial or full rehabilitation, an abutment-level setup is supposed to protect the implant from overload, and counterbalance the misfit between the framework and implant¹⁹⁹. However, in the case of a limited intraoral vertical space, an implant level connection was reported to be the most desirable setup for improving aesthetic and reducing costs^{29,197,389,390}.

Few studies have investigated the clinical outcome of an implant-level screw-retained FPD and/or FCP^{200,206,208,391}. This type of reconstruction requires accurate prosthetic procedures to prevent critical stress in the implant framework interface, especially in ICC¹⁶⁵. Unfavourable stress levels and consequent metal fatigue increase the risk of technical and mechanical complications^{201,392}.

Implant fractures were reported to occur with this type of setup, especially in conditions where Au-alloy-casted frameworks were

screwed at the implant level in ICC, which presented a small diameter and reduced implant coronal wall thickness. Possible alterations in the framework production, caused by laboratory procedures, may introduce misfits in the implant framework mating areas that, under cycling loading, may alter the loading bearing capacity of implants and create cracks²⁰¹.

Implant fractures were reported to be a rare event. Adell² reported 3.5% of implant fractures, which decreased with the increase in the use of Ti alloy in the implant production⁵¹. Balshi³⁹³ highlighted three major categories of causes of implant fractures: (i) defect in implant design or material, (ii) misfit of the prosthetic framework, and (iii) physiological or biomechanical overload. The latter was the most probable cause, as fractured implants reported in Balshi's analysis belonged to patients with parafunction habits.

Another dilemma concerns implant fracture as a consequence versus the cause of marginal bone loss and peri-implant diseases^{394,395}. Even if the incidence of implant fracture has been reported to be a rare event, it is more frequent in FPDs than in FCDs^{12,246}. However, this evidence may be underestimated³⁹⁶.

Mechanical damage of the implant may be caused by critical bending stresses when excessive bone loss has occurred²⁸⁶. Conversely, a pre-existing undetected crack may be the cause of marginal bone loss.

However, in a clinical scenario, the implant microfracture may not be visible in a radiograph image or detected during a clinical inspection. Consequently, bone loss may have been misinterpreted and reported, by the clinician, as a biological complication with peri-implant inflammation status³⁹⁶. Moreover, the effect of fatigue phenomena may not be immediately recognisable and appears after a period of function with just minor or undetectable clinical complications²⁴⁸.

This is the dilemma; it is unclear, if bone loss is a cause or an effect of pre-existing undetectable fractures^{201,202,286,394-396}.

In **Study I**, a misfit was intentionally evaluated in a model simulating a bridge where a Ti-milled implant level framework was screwed into implants with a diameter of 3.5 mm (Figures 17 - 18).

When a framework is connected to an implant, especially with a misfit, stresses are dissipated through all the interfaces that interact in the prosthetic multi-unit implant system.

At the implant-bone interface, stresses may induce a grade of bone remodelling as a result of compensation.

In vitro, *in vivo*, and clinical studies demonstrate that implant displacement occurs, reducing the misfit for total compensation of approximately 20 µm. However, the possible implant movement is more marked when the connection between the framework and the implants forms in the early phase of healing like the immediate loading procedures. Moreover, it is mostly related to the bone-specific composition in quality and quantity. It is difficult to interpret the bone-implant interface in a specific model, the relationship between stress and strain according to the biomechanics and biochemical properties, and the mechanism of the elastic, phasic, and viscous phases of different anisotropic behaviours of the jaws²⁴⁷.

Misfit effects often dissipate within the weakest part of the system in the form of veneering chipping, framework fracture, screw fracture or loosening, abutment fracture or loosening and bone resorption prior to implant fracture²⁴⁶.

It has been reported that ICC exhibits better continuity of yield forces and possesses high rigidity^{149,150} and has a low chance for leakage compared with external hex or internal butt joints^{155,156,397}.

Conversely from an external hexagonal design perspective, ICC implants should have a geometry with specific conical angulation and coronal wall thickness to guarantee frictional resistance of the abutment concurrent with consistent robustness of the implants under loading^{398,399}.

Arguably, ICC implants may present mechanical disadvantages because of the reduced coronal wall thickness and the resultant decrease in bearing capacity, and the use of a screw-retained multi-unit abutment was not considered harmful to the implants in multi-unit restorations²⁸⁶. Lee et al. stated a 0.3 mm wall thickness limit for ICC implants for facilitating load-bearing capacity and preserving the elastic module³⁹⁸.

From mechanical engineering, fracture resistance is inversely proportional to the radius of the test specimen according to the equation of the hollow circle: $I_{(\text{moment of inertia})} = \pi \times (D_o^4 - D_i^4)/64$ where D_o is the cylinder outside diameter and D_i is the cylinder inner diameter of the implant.

However, in the last few years the development of the new Ti alloys and geometrical connection designs have improved the robustness of implants with smaller diameters^{286,400}.

Besides, the potential mechanical damage and weakening of implants do not only depend on the reduced diameter dimension; other aspects play important roles such as the implant framework interface assembly¹⁵¹ and the induction of fatigue during function²⁸⁶.

To detect possible implant failures, three additional aggravating clinical situations were applied to **Study I**: (i) load, (ii) bone-level conditions, and (iii) misfit. The load used, 800 Ncm, conforms to the maximum occlusal force recorded in humans with an implant-supported reconstruction in the molar region⁴⁰¹⁻⁴⁰⁷.

The bone-level condition mimicked two possible clinical scenarios, one with no marginal bone loss and one with bone loss. These values were chosen following the ISO standard 14801:2007³⁶⁹.

The load was transferred to a milled framework that was screwed to the implants seated within two models with or without a misfit, respectively. The magnitude in the misfit was set to 200 μm , which is considered within limits and is clinically acceptable^{28,248,408}. These settings, considered as critical, were applied to evaluate the possible extreme conditions that may influence the behaviour of implants.

In **Study I**, the misfit was visible and a grade of strain was detectable during screwing for obtaining the final position of the framework (Figures 17 - 18). The fatigue theories with dynamic load were used in a model since this was considered to be a more clinically relevant method than static fracture tests⁴⁰⁹.

In **Study I**, the conservative approach of Goodman's theory was used to underestimate the fatigue life of implants. This was done to incorporate a potential error in the model setup³⁷¹. This theory calculates effective stress, based on the stress amplitude and mean stress, that could be equated to S-N curves of fully reversed load; i.e., the mean stress is 0. The fatigue limit, at 1×10^6 cycles, of Ti Gr 4 has been reported to be close to 50% of the UTS. This is in the same range used in **Study I** (Figure 9), indicating that the offset approach for the fatigue data presented by Chandran is reasonable²⁵³.

The 4 groups in **Study I** were tested with the same FEA setup and this simulation neglected fatigue life dependencies such as surface treatment and stress concentration factors (i.e., notch effects).

The findings showed a pattern of effective stress concentration along all implant-framework connections. These results corroborated what was previously reported in a study that simulated different grades of misfits, in an implant level connection setup²⁰².

In **Study I**, the misfit/no bone loss group, presented a vertical region of effective stresses above the fatigue limit (Figure 22).

The high stress may penetrate through the wall thickness and initiate a fatigue crack (Figure 22 A-B). These highly simulated effective stresses of the misfit/no bone loss group coincide with the location of the crack detected at the SEM and the CT-3D (Figures 19 - 20). The bone loss groups, in contrast with the misfit/no bone loss group, presented areas of high simulated and effective stress that did not appear to penetrate through the wall thickness.

From the current FEA findings, when misfit is present, implants without bone loss may have an increased risk of vertical fracture compared to those with bone loss.

The findings from the fatigue loading model showed that only one implant out of 32 presented with signs of material failure. One crack (Figure 19) was detected using SEM analysis at the inner surface of 1 implant out of 8 in the misfit/no bone loss group; findings were confirmed in the CT-3D analysis, where the crack engaged the implant wall (Figure 20).

Several explanations on why only one sample resulted in a crack, during the physical test while the FEA presented a lifetime less than 1×10^6 cycles above 375 MPa are listed as follows:

(i) Goodman's theory, being conservative as previously explained, possibly underestimated the fatigue life.

(ii) In the case of marginal bone loss, the implant may have adjusted to the final position, hence reducing the simulated effective stress. This may explain why no cracks were found in the samples of the bone loss groups after the fatigue test.

(iii) The discrepancies in results between the mechanical test and FEA simulation were not completely unexpected as observed by Yamaguchi et al.⁴¹⁰, who reported that fatigue tests may fail to identify the crack initiation site.

(iv) The screw preload maintained a minimum force of 250 N in the conical portion of the implant that decreased the alternating stress. This could explain why only one sample presented a crack, despite the high load of 800 N.

From the findings from **Study I**, implant fracture is an infrequent adverse event, even when a misfit is present, and this confirms the clinical evidence. However, the results suggested that implant fractures may occur when fixtures are fully supported by marginal bone, supporting the claim that cracks occur before bone loss. Therefore, it may be speculated that secondary bacterial contamination of undetected fractured surfaces will cause a rapid bone breakdown.

The location of high-stress areas, as reported in the simulation analyses, must be accurately evaluated by the clinician when implant level FPD is chosen as the treatment. Moreover, if unfavourable clinical conditions such as parafunctional habits and/or implants angulation that exceeds the conical total axis degree deviation persist (Figure 34), an abutment-level connection should be recommended.

To the best knowledge of the author of this thesis, no study evaluating the effect of a misfit on an implant-level setup with ICC in terms of mechanical or biologic risks was found²⁴⁷, as presented in **Study I**.

Figure 34. Implant vertical fracture in both the implants. The fracture was not clearly visible at the X-ray analysis.

Hard and soft tissue changes in FPD. (Study II)

In **Study II** MBL change was the primary outcome. The null hypothesis was rejected since a statistically significant difference was observed between prosthetic delivery of the implants in the IL and AL groups at 6-month and 1-year follow-ups. However, the magnitude of the bone loss between the groups may be of limited clinical relevance since after 1 year it was 0.086 ± 0.313 mm and 0.005 ± 0.222 mm for the IL and AL groups, respectively (Table 21) (Figure 25).

These findings were confirmed by Todisco et al.²⁰⁸ in a study involving two central implants, in a 4-implant immediate mandible rehabilitation, that were randomly allocated to groups with or without a multi-unit abutment connection. Data showed a statistically higher bone loss during the first year in the IL group than the abutment level group: 0.17 ± 0.27 mm versus 0.002 ± 0.09 . After 3 and 5 years, there were no further changes in MBL between the two groups.

Gothberg et al. verified the same trend²⁰⁷. In an RCT with partial segments that were rehabilitated with an immediate or conventional loading protocol, the 1-year bone loss was reported to be statistically higher in the implants without abutments than in those with abutments. This difference in bone loss was also present after 3 and 5 years, but only in the conventionally-loaded implants group³⁹¹.

Same trends were confirmed by another RCT study in which edentulous patients were randomly allocated to receive a fixed reconstruction with an implant level screw retained or cement retained retention. In this study the authors reported a bone loss of 1.01 ± 0.33 mm and 1.23 ± 0.45 mm for screw and cement retained restoration after 1-year respectively with minor slight increase over the 8-year follow-up visit⁴¹¹.

In **Study II**, at the BL, the recorded PI was very low (0.4%) and subsequently it increased to 9.9% and 13.9% at 6 months and 1-year respectively.

Interestingly, BoP increased in the IL group while decreased in the AL group with time (Table 13). The mean PPDs at the BL at 6 months and 1 year were higher in the IL for all the sites at all follow-up time points, and this was statistically significant. Moreover, the PPD significantly decreased with time in the AL group, but not in the IL group (Table 14).

These findings are in line with a 5-year clinical trial, investigating the use of an intermediary abutment in a full-arch rehabilitation. After 5 years of loading, BoP was statistically higher in the abutment-free group²⁰⁸.

One possible explanation for the difference between hard and soft tissue parameters of the AL and IL groups in **Study II** may be related to the prosthetic steps that could have interfered with the healing of the supra-crestal compartment in the IL group.

Some clinical procedures could inhibit the maturation phase of the soft tissue and impair the formation process of the connective layer.

Abrahamsson et al.⁴¹² reported that the repeated abutment change interferes with marginal bone maintenance. The authors demonstrated that implants submitted to repeated dis-/reconnection (once every month for 5 times after abutment connection) presented marginal bone loss. Thus, as shown by Berglundh and Lindhe⁴⁵ in the histomorphometrical analysis, as a consequence of bone resorption, an inferior position of the connective tissue was maintaining the supra-crestal tissue dimension. These findings were corroborated in another animal study that reported that dis-/reconnections of the abutments (twice at 4 and 6 weeks) altered the soft and hard tissue dimensions within 8 weeks from implant placement⁴¹³.

The maturation of the soft tissue is a gradual process and takes 6-8 weeks to be completed^{43,44}.

It could be that, in the IL group of **Study II**, the repetitive soft tissue disruption exposed the peri-implant compartment to bacterial contamination¹⁵⁷. This resulted in worsened inflammatory status and, eventually, a more pronounced marginal bone resorption as reported in **Study II** and corroborated by Todisco et al.²⁰⁸ and Gothberg et al.²⁰⁷.

Contrarily, in another experimental study performed by Abrahamsson et al.⁴¹⁴, the single change from a healing abutment to a definitive abutment, compared to an immediate placement of the final abutment at the second stage surgery, did not interfere with the supracrestal compartment or with the MBL. These findings were confirmed by Borges et al.⁴¹⁵; in an RCT, abutments connected during implant placement or at the second surgery were compared, and no difference in MBL change was observed between the two groups.

In **Study II**, the implants in the AL group, in contrast with the IL group, were connected with the abutments at the second surgery and then never removed. This procedure may allow the soft tissue to create a mucosal barrier and protect the underlying osseointegrated implant.

In a systematic review on the influence of abutment disconnections on bone loss⁴¹⁶, a significant difference of 0.3 mm of higher bone loss was present in implants subjected to frequent disconnections. However, data has to be taken into consideration with caution and the clinical relevance of 0.3 mm of bone loss is limited.

The soft tissue barrier disruption by prosthetic procedures is also debated. Consequently, clinicians have proposed methods allowing immediate insertions of abutments at the time of surgery without subsequent removal⁴¹⁷⁻⁴¹⁹. While peri-implant soft and hard tissues may be more stable with one-time abutment procedure⁴²⁰, data from reviews and metaanalyses reported unsatisfactory outcomes with inconclusive clinical recommendations, mostly because of the lack of adequately designed RCTs⁴²¹⁻⁴²⁴.

Another aspect that was pointed out was the response of the peri-implant tissue to the different material compositions of the abutment. The peri-implant tissues of **Study II** were in direct contact with the Ti abutment in the AL group, while in the IL group, tissues faced the Co-Cr framework. The quality and quantity response of the peri-implant tissues to abutment material composition was analysed in animal studies. The apical migration of the crestal bone was shown to be statistically significantly different when Au-alloy abutments were used compared to the Ti and Zi^{425,426}. Moreover, the quality assessment of the cell compositions reported statistically higher leukocytes and lower collagen fibres and fibroblasts at 2 and 5 months in the Au-alloy abutments compared to the Ti and Zi ones⁴²⁶.

In **Study II**, Co-Cr material was compared to Ti in a peri-implant environment and, to the best knowledge of the authors, reported for the first time in a human setup. Even if Co-Cr is considered biocompatible, an *in vitro* study reported that the viability of the epithelium cells and fibroblasts were inferior compared with Ti⁴²⁷.

However, there is still no strong evidence on this and on the clinical outcome regarding the response of hard and soft tissues to Co-Cr material.

The KM was analysed in **Study II** and buccal keratinised mucosa was likely to decrease with time (Table 15). However, no correlation between the width of KM and MBL change was reported.

Hard and soft tissue changes in FCD and IOD. (Study III-IV)

The MBL change was the primary outcome investigated in **Study III**, while in **Study IV**, it was analysed as secondary outcome.

When the MBL change within the groups and over time was considered, no statistically differences were observed within the groups and over time.

The difference in MBL change between the two groups was less than 0.4 mm which was defined as the threshold for the null hypothesis which was not rejected (Table 22). The difference in MBL change within the same group and between the two groups of comparison during 3 years was clinically irrelevant. The trends of MBL change found in **Study III** are consistent with those found in the literature for the same implant system and similar prosthetic design (Tables 29 - 30 - 31). Engquist⁴²⁸ reported no MBL changes between 1 and 3 years in 17 patients treated with 104 implants conventionally loaded in the maxilla.

Collaert and De Bruy³⁸⁸ treated 25 edentulous patients in the maxilla with seven to eight implants immediately loaded. The MBL was 0.65 ± 0.57 mm at 6 months with no further significant changes within the following 3 years. The two authors reported an equilibrium phase after 6 months of healing. With the same implant system used in this thesis, Thor et al.⁷¹ reported findings involving 51 patients who were immediately loaded in the maxilla with 306 implants. The MBL change presented a bone loss of 0.45 ± 0.73 mm after 6 months of function and 0.44 ± 0.79 mm and 0.57 ± 1.12 mm of bone loss at 1 and 3 year(s), respectively.

The same trend on MBL changes has been observed with different implant systems such as Straumann® Tissue Level implants. In a 2-year clinical trial, 25 edentulous maxillae were rehabilitated with 146 implants. It was reported a mean bone loss of 0.24 mm and 0.15 mm at 1 and 2-year respectively³¹⁶. With the same implant system 24 edentulous patients in the maxilla were restored with 142 implants to support FCDs. The MBL was at 2.13mm at the BL, 2.54 mm at 1Y and 2.68 mm at 3Y⁴²⁹.

Table 29. Conventional Loaded Implants (AstraTech Implant System) in edentulous maxilla. Mean Marginal Bone Level (MBL), Bone Loss and Marginal Bone Level Change (MBLC).

	Engquist 2002 ²⁴³ Åstrand 1999 ¹¹⁵ , (1y report) Tioblast	Rasmussen 2005 ⁶ Tioblast	Veltri 2008 ⁴⁹² Tioblast	Hjalmarsson 2011 ²⁰⁰ Tioblast IL connection Retrospective	Mertens 2012 ¹¹ Tioblast Cohort	Ravall 2013 ⁴³¹ Åstrand 2004 ⁴³⁴ (5y report) Tioblast smooths collar RCT	Slot 2016 ¹¹² Slot 2013 ⁴³² (1y report) OsseoSpeed 4x6 Implant IOD RCT	Boven 2017 ⁴⁹³ same cohort Slot 2013 ⁴³² OsseoSpeed Retrospective
	RCT MBL MBLC patients /implant	Cohort MBL Bone Loss from surgery patients /implant	Cohort Bone Loss from surgery patients /implant	Retrospective MBL MBL patients /implant	Bone Loss from BL patients /implant	MBL Bone Loss from BL patients /implant	Bone Loss Bone Loss 41 61 from BL patients /implant	MBLC MBLC Anterior Posterior patients /implant
Surgery	17/104	16/91	12/73	35/213	16/	16/	50/250	50/250
Ab. Connection	-0.70 (±0.33)	0.2 (±0.31)	1.2/73	ceramic resin				
Baseline	1.45 (±0.24)	0.2 (±0.20)	0.30 (±0.13)		1.47 (±0.26)	1.70 (±0.26)	0.24 (±0.32)	0.25 (±0.29)
1 year	1.67 (±0.24)				1.75 (±0.34)	1.91 (±0.37)	0.50 (±0.37)	-0.23 (-0.78; 0.00)
3 year	1.68 (±0.33)							-0.69 (-1.14; -0.13)
5 year								
7 year		1.27 (±1.15)						
8 year								
11 year								
12-15 year								
≥ 2mm Bone Loss	6%	96.6% (max)	1%	19.1% 25.6%	4.2% 7.5% (5Y)	6%	2%	8.7%
Implant survival rates	98.2%	97.2% (mand.)	100%	98.6%	96.8% (11Y)	95.5% not specified (mandible/ maxilla)	99.2%	97%

Table 30. Immediate Loaded Implants (AstraTech Implant System) placed in edentulous maxilla. Mean Marginal bone level (MBL), Bone Loss (BL) and Marginal Bone Level Change (MBLC).

	Collaert 2008 ³⁸⁸	Barbier 2012 ²⁰⁶	Pieri 2012 ³¹⁴	Toljanic 2016 ⁴⁹⁵ , (1-5-year) Thor 2014 ⁷¹ , (3-year) Toljanic 2009 ⁴⁹⁴ , (1-year) Osseospeed	Toljanic 2018 ⁴⁹⁵ , (1y report) same cohort Toljanic 2009 ⁴⁹⁴ Osseospeed /Tilted	Trabakonic 2019 ⁷² Swedish cohort Thor 2014 ⁷¹ Osseospeed
	Tioblast baseline after Implant placement	Osseospeed Half implants in post-ex site baseline after 6 months Implant level connection of functional loading	Osseospeed after Sinus Lift baseline after Implant placement	baseline after surgery		baseline after surgery
	patients /implant	patients /implant	patients /implant	patients /implant	patients /implant	patients /implant
	MBL	Bone Loss	Bone Loss	MBLC	Bone Loss	MBLC
	Bone Loss	Bone Loss	Native bone		posterior Implants	
Surgery					axial	
6 months	25/195 0.07 (±0.10)	20/120	20/155	51/306	51/306	25/150
1 year	24 0.65 (±0.57) 0.58 (± 0.58)			- 0.45 (±0.73)		
2 year	25/195 0.67 (±0.54) 0.60 (± 0.53)	20/118 0.35 (±0.29)	20/153 0.46 (±0.25)	47/280 - 0.44 (±0.79)		2/132
3 year	24 0.70 (±0.61) 0.63 (± 0.61)			46/274 - 0.37 (±0.82)		2/132
5 year	22/172 0.79 (±0.64) 0.72 (± 0.63)			45/267 - 0.57 (±1.12)		2/132
≈10 year				40/232 - 0.44 (±1.25)	0.14 (±0.34)	2/132
	SUCCESS AT 86% < 1.5 MM AFTER 3 YEARS 8.7% 1.5-2.5 2.9% 2.5-3.5 2.3% 3.5-5		98.7% 100%	1Y 96.1% 3Y 95.7% 5Y 93.2%	89%	81.9%

Table 31. Augmented Bone, Conventional Loaded Implants (AstraTech Implant System) placed in edentulous maxilla. Mean Marginal bone level (MBL), Bone Loss and Marginal Bone Level Change (MBLC).

	Thor 2005 ⁷⁷				Hallman 2005 ⁴⁹⁶		Boven 2015 ⁴⁹⁷ same cohort Slot 2013 ⁴³² IOD Osseospeed			
	Tioblast Test (PRP)				Tioblast		IOD Osseospeed			
	patients /implant	Bone Loss All implants	Bone Loss Posterior Implants		patients /implant	Bone Loss	patients /implant	Bone Loss Native bone	Bone Loss Augmented implant length <2/3	Bone Loss Augmented implant length >2/3
Surgery	19/152	Test	Ctrl	Ctrl	11/74Astra		26/116	40 implants	16 implants	60 implants
Baseline		1.3 (±1.9)	1.5 (±1.7)	2.7 (±1.0)				-0.1 (- 0.4; 0.0)	0.0 (- 0.2; 0.0)	-0.2 (- 0.5; -0.1)
1 year		1.8 (±1.1)	2.0 (±0.9)	3.7 (±0.9)				-0.4 (- 1.0; -0.0)	-0.2 (- 0.9; 0.0)	-0.5 (- 0.8; -0.1)
5 year						2.3 (±0.8)				
Implant survival rates		98.7%				87%	99.1%			

Moreover, the same magnitudes of MBL changes as reported in **Study III** were stackable when a different implant system was used (Nobel Speedy Groovy implants, Nobel BioCare AG, Balsberg, Switzerland). Tallarico et al.⁴³⁰ evaluated 40 patients randomly allocated to receive 4 or 6 implants in the maxilla, immediately loaded with an FCD. The difference in MBL change between the two groups had of limited clinical relevance at 0.20 ± 0.06 mm between 0-60 months. However, a steady increase of bone loss in each group over time was noted and even the major magnitude was reported to take place during the early stage of treatment.

As far as the author of the present thesis is aware, this study is the only RCT on maxillary FCD to compare the use of four or six implants.

Interestingly, in **Study III**, there was a statistically significance difference in MBL between the 4-I (0.30 ± 0.50 mm) and 6-I (0.14 ± 0.32 mm) groups. An explanation could be related to the different stress distribution of the interim prostheses. The temporary CD which was realigned and placed over the healing caps inserted at the second stage surgery. It can be speculated that the CD might have had a better stability in the 6-I group compared to 4-I group. It was reported, in **Study III**, that it took $8 (\pm 2)$ weeks from the second stage surgery until the delivery of the final reconstruction. During this period, the bone-to-implant-interface is considered to still be in a modelling-remodelling phase with the consequence that the marginal bone of the implants in the 4-I group may have been hampered by different loaded stress of a less stable interim realign prostheses compared to the 6-I group.

Moreover, at the subject level, an MBL equal to 0 (meaning subjects whose implants had bone located at the reference point) was reported for 35.7% at BL, 28.6 % at 1 year and 20.4% at 3 years (Figure 28).

The bone loss with time is well-documented. Rasmusson et al. reported a bone loss of 0.28 ± 0.20 mm at 1 year and 1.27 ± 1.15 mm at 7 years⁶. Hjalmarsson reported a bone loss between 1.00 ± 1.01 mm and 1.30 ± 1.0 mm at 5 years²⁰⁰. Mertens and colleagues¹¹ reported mean bone losses of 0.25 mm, 0.30 mm, and 0.56 mm at 5, 8, and 11 years, respectively (Table 29).

Ravald et al.⁴³¹ reported bone losses of 0.39 ± 0.20 mm at 5 years and 0.7 mm between 12 to 15 years. Slot et al^{112,432} reported a

doubled magnitude of bone loss between 1 and 5 years. Trabakonic reported bone losses of 0.19 ± 0.40 mm, 0.75 ± 0.92 mm, 0.61 ± 1.19 mm, and 1.29 ± 2.47 mm at 1, 3, 5, and 8 to 10 years, respectively. The authors reported that implants placed in bone quality type 4³⁷⁹ presented with significantly higher bone losses compared to bone quality type 3 (Tables 29, 31).

Using Straumann® Tissue Level implants in a 10-year study where 16 and 8 patients were enrolled to receive an early loaded and conventionally loaded FCDs, respectively, bone losses of 0.24 mm, 0.39 mm, 0.71 mm and 1.07 mm from base-line to 1, 3, 5, and 10 years, respectively, was reported⁴³³.

Even if the larger proportion of MBL changes is reported to be during the first year of function, a late remodelling process is present, and some implants may not reach the equilibrium phase and show no signs of corticalisation². Åstrand et al.⁴³⁴ reported an increase in the distinct cortical border over time in AstraTech implants placed in the maxilla, from 11% to 35% in a prospective 5-year follow-up. However, 53.4% of the implants did not reach a complete corticalisation, especially in the maxilla (Table 32).

Table 32. Different cortical shape in two implant system over 5-years⁴³⁴

	Maxilla				Mandible			
	Baseline		5-year		Baseline		5-year	
	n	%	n	%	n	%	n	%
Astratech Implants								
Diffuse	170	88.5%	94	53.4%	102	70.3%	31	19.4%
Distinct	21	11.0%	62	35.2%	42	29.0%	50	31.3%
Cortical	1	0.5%	20	11.4%	1	0.7%	79	49.3%
Brånemark Implants								
Diffuse	88	46.6%	19	10.3%	41	29.1%	13	8.6%
Distinct	101	53.4%	121	65.8%	100	70.9%	57	37.5%
Cortical	0	0%	44	23.9%	0	0%	82	53.9%

The implant survival rates in **Study III** were very high in both groups (99.4% and 100% for the 6-I group and 4-I group, respectively) and were comparable with those of similar reports in the recent literature on maxillary implants^{11,230,429,430}. When selecting a rehabilitation

approach with a reduced number of implants, as in 4-I group, one concern is that losing a fixture may require an extra surgical procedure to substitute it, while this is often considered unnecessary if the treatment strategy already involved 6 implants. In fact, the only patient that experienced implant loss in the present study (6-I group) could successfully be rehabilitated on the 5 remaining implants without additional surgeries. It can be argued that, when considering the low incidence of implant failures as reported in the literature, it might be an over-treatment to insert a higher number of implants than needed just to account for possible failures⁵⁰.

In the 1980s and the 1990s, one of the major issues involving the number of implants to be used for edentulous patients was the early failures, up to 10%, after implant placement and more frequently reported in the maxilla^{2,53,56,57,73}. This drawback was mainly related to the machined surface characterisation which could inhibit the biomechanical bonding in the early phases of healing^{20,435}.

With the introduction of moderately rough surfaces, early implant failure decreased in general, especially in the maxilla. As reported in a retrospective study over a period of 28 years, implant failure decreases in the maxilla from an average of 11.5% (for implants inserted between 1986-2002) to 2.1% (for implants inserted between 2003-2012) due to the difference surface characterisation⁴³⁶. Thanks to this achievement in the field of osseointegration Malo et al. proposed the 'all-on-4®' concept for the treatment of edentulous maxilla with implant survival rates after 13 years of service of 94.7%^{137,437}.

Moreover, even if the use of fewer than four implants for a maxilla FCD is debated there are reports of successful edentulous maxillary rehabilitations on three or even two implants^{87,91,438}.

Regarding the medium-term marginal bone stability, good results were reported in both studies. In **Study IV** MBL was 0.30 ± 0.40 mm at BL and 0.27 ± 0.35 mm at 2-year follow-up and the change was associated with a bone gain of 0.02 ± 0.22 . This finding is similar to what was presented in **Study III** where the MBL change in all the implants pooled was 0.01 ± 0.32 mm and 0.03 ± 0.37 mm between BL and 1 year and BL and 3-year follow-up, respectively (Table 24).

These findings suggested that since hard tissue was stable during the years, both types of rehabilitations could be considered as valuable treatment options for edentulous patients.

Soft Tissue index

In **study III**, the implants in the 6-I group presented a higher PI than the implants in the 4-I group at 1-year and 3-year (Table 16). This difference could indicate that it is more complicated for the patient to perform care maintenance on 6 implants than on 4 implants. This is probably also due to the proximity of the implants in the 6-I design group^{438,439}. This verifies what was reported by Slot and co-authors¹¹², namely that the PI was statistically significantly higher in the 6-implant group compared to the 4-implant group. The authors stated that with more implants, patients have to follow a stricter self-care hygiene regime.

One critical aspect to consider when proposing fixed bridges is a certain difficulty in hygienic maintenance experienced by patients and it has to be reported that the extent of reconstruction has an influence on the presence of plaque. In this thesis, the presence of a lower level of plaque in patients with implant supported FPD (**Study II**) compared to FCP (**Study III**) was consistent with a systematic review where the peri-implant condition was examined between the two groups of treatment options⁴⁴⁰. Despite the hygienic recalls performed in this study, inadequate plaque control was observed in both groups of **Study III** in a relevant number of implant sites with an increase after a longer follow-up period (Table 16). Moreover, visible plaque was observed in the majority of the rehabilitations (27 prostheses at 1Y and 33 prostheses at 3Y) (Table 25).

Based on these results, the patient self-provided hygienic maintenance might be easier in the 4-I group compared to the 6-I group in **study III**. For these reasons, a 4-I FCD may provide an easier cleanability to fixed rehabilitation of the edentulous population⁴³⁸. Moreover, the total cost of 4-I treatment implies a reduced financial burden for patients or services and bone regeneration procedure might not be necessary, thus also reducing the surgical invasiveness. From a cost-effective point of view, it can be argued that a 4-I solution may be more appropriate for the edentulous maxilla⁴⁴¹.

In **Study IV**, plaque was present at the 2-year follow-up on 7.4% of the surfaces. No statistically significant differences were observed between BL and 2-year. A possible explanation could be related to the retention of the prostheses. Since the prostheses are removable, it facilitates self-cleaning. This statement was corroborated by a

study involving an RCT that compared the outcomes of using 4 or 6 implants to support an IOD in the maxilla and the authors reported a low percentage of PI¹¹².

Further explanation of the lower PI score in **Study IV** compared to **Study II** and **III** could be related to the index scale used. In **Study II** and **III** a mPII by Mombelli³³¹ was adopted while in **Study IV**, a yes/no dichotomous variable was used.

As a matter of fact, Slot and co-authors¹¹² reported the PI as a dichotomous variable, as in **Study IV**, however, in the study published in the 2019 by the same authors¹¹³, the parameters were evaluated in accordance with Mombelli et al.³³¹. Similarly with is reported in **Study III**, the PI reported by Slot et al. had means of 21% and 27% at 1 and 5 years, respectively¹¹³. The more precise the parameters, the higher the indexes are²⁶⁹.

In **Study III** a higher BoP was registered at BL in the 4-I group compared to the 6-I group being 41.1% and 29.6%, respectively at BL (Table 17). This could be related to less stable hard and soft tissues and explained by the higher difference in MBL of the 4-I group compared to the 6-I group (Table 22).

In **Study IV**, there was a statistically significant difference between BoP at BL (15.41%) and at 2-years (22.30%). BoP in **Study III** and **IV** was not correlated with bone level alteration, which is consistent with what is reported in literature^{321,322}.

In a retrospective clinical trial performed by Lekholm et al., 20 patients were followed for a mean period of 7.6 years, that 80% of the sites with BoP did not present with progressive bone loss. The authors concluded that the radiological evidence and the microbiological and histological findings showed healthier implants regardless of the findings derived from the clinical indexes⁴⁴². These data are consistent with a systematic review that analysed the correlation between the biological parameters and the implant survival and prevalence of peri-implantitis. The papers included in this review reported a high variation in BoP between 4.7% and 95.0% with a weighted mean of 52%. The authors reported that BoP and PPD was not correlated with bone loss³²³.

In **Study III**, a slightly lower PPD was observed for the 6-I implants compared to the 4-I implants at all timepoints. The difference, is of little clinical relevance, being less than 0.3 mm. The reduced probing

is mainly due to a better stability of the soft tissue over time in the 6-I group in the early phase before the delivery of the final FCD. Similar data were reported in **Study IV** where the PPD presented no difference between BL and 2-year follow-up with a mean average of 2.46 mm.

These data were consistent with a previous prospective reporting a reduction of PPD over time with a mean of 2.9 mm after 3-year⁴⁴³. Furthermore, Pieri et al.³¹⁴ reported a decrease in PPD in 20 patients, rehabilitated with an FCD maxilla, using the same implants system as in **Study III**.

It has been stated that probing an implant pocket is an essential diagnostic tool to evaluate the 'tonus' of the peri-implant tissues and, it has been argued, that bleeding should be considered as '*an approximation of the true condition*' of the peri-implant status³²⁶.

However, despite the doubted relevance of the perio markers³²⁰⁻³²³ it has to be noted that maintenance is essential for the success of implant therapy³³⁵.

The KM was analysed in **Study III** and, in general, there was a likelihood of a decrease in buccal keratinised mucosa with time in both groups (Table 19) (Figure 24).

The importance of KM has been debated and its absence was claimed to be related to increased (i) inflammation of the peri-implant mucosa and (ii) bone loss¹⁷⁴. Moreover, it seems that more than 2 mm of attached mucosa prevents plaque accumulation especially in patients with a deficient oral self-maintenance regime⁴⁴⁴ and results in improved comfort for the patient during brushing⁴⁴⁵.

In the evaluation of the hard and soft tissue change over time, the influence of some clinical aspects was considered, such as the use of a transmucosal abutment, the implant inclination, and the presence of a cantilever.

The screw retained one-piece transmucosal abutment used in this study may be considered as one explanation for the low values of MBL change. It was reported that this type of abutment possesses a greater resistance to bending forces than a two-piece one¹⁵¹. In a recent systematic review and meta-analysis, it was reported that bone loss was statistically higher in angulated abutments compared to straight ones. The authors addressed the amount of disconnection and re-connection, the design of the implants and the height of the

abutment as possible explanations⁴⁴⁶. In the same manner, in **Study III** as in **IV** and as previously reported in **Study II**, the abutment was seated at the second surgery and never removed, thus limiting the number of disconnections and re-connections. Moreover, the abutment design presents a straight profile, which facilitates an immediate positioning⁴⁴⁷.

In **Study III**, the height of the abutment that was most suitable for prosthetic restoration and mucosal thickness was chosen. No difference in MBL change was noted regardless of the height of the abutment used. This data was confirmed in a one-year RCT, where a parallel set up was used to compare the bone loss. Three groups of patients were compared. Two groups received two different abutments heights (1-2 mm) immediately connected during the first surgery, and a third group of patients received 2 mm abutment height at the second surgery. No differences were observed regardless of the height of the abutment or the connection time⁴¹⁵.

However, other findings suggested that there may be a correlation between bone loss and the height of the abutments²⁸⁹.

Windael et al. in a 10-year report⁴⁴⁸ observed that short abutments (0-1.5 mm) presented with significantly greater bone loss (0.60 mm) compared to higher abutments (≥ 3 mm), for which bone loss was 0.04 mm. This trend was confirmed by other authors²⁸⁹. In a 2-year clinical study, where two splinted or unsplinted implants were used to support a mandibular IOD, a significantly higher bone loss was reported when implant had short abutments. In particular, the changes in MBL were 1.17 mm, 0.86 mm, 0.38 mm and 0 mm at 1-year and 1.23 mm, 1.03 mm, 0.41 mm and 0 mm at 2-year with abutment heights of < 2 mm, 2 mm, 3 mm and ≥ 4 mm, respectively. The authors concluded that short abutments, used in implant sites where soft tissue thickness was limited, provoked bone loss that is possibly due to the establishment of the supra-crestal vertical dimension⁴⁴⁹.

Additionally, Galindo-Moreno et al.⁴⁵⁰ stated that an abutment height of 2 mm was the minimum requested distance from the ridge crest to prevent bone loss. Besides, the two above studies reported that the vast majority of the bone losses occurred during the first year of loading^{449,450}.

In another RCT, where short and long abutments were compared, it was reported that regardless of the vertical mucosal thickness

(≤ 2 mm; ≥ 2 mm) a shorter abutment (1 mm) presented more bone loss in comparison to a higher abutment (3 mm). Again, more bone loss was reported to occur within the first 6 months of healing⁴⁵¹.

In this study, the implants were subjected to approximately 4 dis-/reconnections⁴⁵¹. This type of prosthetic procedure, which differs from what was clinically performed in **Study II, III** and **IV**, as in other studies^{414,415}, may have disturbed the supra-crestal soft tissue in the shorter abutment group when compared to the higher abutment group. In the group of patients with higher abutments, the increased space (3 mm) may have rendered the tissues more capable in finding their dimension regardless of the prosthetic dis-/reconnections.

Thus, the soft tissue may have reached the equilibrium phase earlier in the higher abutment group compared to the short abutment group, which presented with less inflammation.

Inversely, the absence of sufficient space in the shorter abutment group hampered the attempt to establish a proper vertical dimension resulting in a traumatic process provoked by the prosthetic dis-/reconnections closer to the bone crest and the consequent increased bone loss compared to the higher abutment group¹⁵⁷.

Based on the above-reported findings, it can be speculated that, if a short abutment has to be used, maintaining fewer prosthetic steps is better for peri-implant tissue healing.

In **Study III**, no difference in MBL change between straight and tilted implants were registered when all the implants were pooled together or in the two groups separately. These findings are corroborated by several clinical studies and reviews that have reported that the inclination of the implant does not worsen the clinical outcome, in terms of implant survival or bone loss^{124,452-455}. Several inclinations (between 15° and 90°) of the implant longitudinal axes in relation to the occlusal planes are provided in literature¹²³. In **Study III**, an implant was considered tilted if it had a mesiodistal inclination of 15° or more. However, this cut-off might not reflect the clinical situation accurately. An implant inclination only describes two dimensions in the mesiodistal direction, as on the radiographs, and does not account for the real three-dimensional implant positions. Moreover, in **Study III**, the operators attempted to restrict the implant inclination to within 45°, which is the maximum recommended angle for the use of the one-piece transmucosal abutment.

The MBL change of the distal implants supporting a cantilever was compared to the straight implants and no statistically significant difference was noted in either **Study III** or **IV**. These data corroborated a previous study in which it was reported that the effect of a cantilever did not affect the MBL change with time^{317,456}.

Patients' satisfaction when treated with FCDs and IODs (Study III-IV).

There is a steady increase in the focus on the patient's wishes as well as a greater interest in the patient outcomes (PROMs). The clinician's perspective on the best treatment plan, in terms of the number of implants and prosthetic design, may not meet the patient's expectations^{457,458}.

Edentulism patients are the most studied population when it comes to attempting to better understand which treatment of a new CD, an IOD or a FCDs could be the most appropriate treatment option³⁶⁸. However, even if the OHRQoL increased after treatment has fulfilled patient requests, the satisfaction of the patient may be not completely addressed.

Satisfaction is a general term and is used in studies to denote an improvement in quality of life. However, in a recently published systematic review, it was explained that measuring the quality of life with a PROM instrument is not the same as defining the satisfaction of the patient examined³⁴⁸. Satisfaction is achieved when the patient's expectations are as closer to being completely realised as possible. Being satisfied, implies a psychometric analysis which depends on the patient's characteristics, in particular, as defined by Sitzia, as the *(i) age or educational attainment, (ii) influence of the environmental, and (iii) socio-psychological phenomena, such as self-interest (the Hawthorne effect) and setting of the treatment (university or private center)*^{351,364}.

Many studies are comparing the level of satisfaction after the treatment of edentulism. Undoubtedly, patients treated with IOD are more satisfied compare to patients treated with CD^{100,357,362,365,366,368}.

The FCD treatment option should be considered as the preferred choice since patients are more likely to feel that a fixed prostheses is a part of their body³⁶⁸. Comparing three groups of patients treated with CD, IOD and FCD, showed that the two latter groups were more satisfied than the CD population and the FCD group showed higher satisfaction rates compared to the IOD group³⁶⁸.

However, another cross-sectional study compared the same three different groups of patients with CD, IOD and FCD, and a greater satisfaction was noticed in patients who received implants³⁶¹.

When it comes to assessing the improvement in OHRQoL of patients with IODs compared to FCDs, results are more inconsistent especially for maxilla restorations^{203,361}. In the studies published by Brennan et al.⁴⁵⁹ and Katsoulis et al.²⁰³, a slightly higher satisfaction was recorded in patients with FCDs, specifically from a psychological standpoint. Martínez-González et al.³⁶³ noted an overall higher satisfaction with FCD, but the difference between the single items of the questionnaire was not statistically significant. In addition, patients with overdentures showed better ability regarding hygiene maintenance. The data of this article seems to corroborate the PI score in **Study III** and **IV** were the latter ones demonstrated a better oral hygiene maintenance. Moreover, it has to be noted that in **Study III**, the ability for cleaning the interim plant area of the prostheses was limited, since, 27 patients (48%) at 1 year and 33 patients (59%) at 3 years presented plaque.

The same phenomenon was reported in a study where among 20 interviewed patients, rehabilitated with an FCD in the maxilla, 45% reported difficulties in the cleaning procedures³¹⁴. Martínez-González et al.³⁶³ corroborated these findings as patients treated with an FCD reported difficulties in cleaning and presented halitosis compared with patients treated with an IOD or a new CD.

A systematic review⁴⁶⁰ conducted in 2015 analysed the PROMs from 84 studies and showed that implant-supported IOD can lead to a higher patient satisfaction of the patient and improved OHRQoL when compared to traditional mandibular CD. On the other hand, another study was not able to show the same success for maxillary overdentures, in patients who previously did not complain about their traditional CD⁴⁶¹.

Although the FCD occupies less space, an investigation of the different types of rehabilitation (CD, IODs and FCDs) in the maxilla, failed to prove a better-reported sense of taste in the rehabilitation without the palatal. Patients with a new CD were equally satisfied as patients with implant-supported IOD or FCD⁴⁶².

These findings are corroborated by others several studies showing that when comparing PROMs of IODs and FCDs, the latter did not demonstrate any significant advantage over the former^{348,361,463}. This could be explained by the fact that patients usually undergo more invasive and longer procedures, and thus spend more money, for

a FCD²²¹. But they are also able to maintain a better oral hygiene with IODs^{368,464}. In addition, PROMs can be affected by several factors, including heterogeneities among study methodologies and populations.

In **Study III** a limited general questionnaire was delivered to patients, as reported in a previous study published by Mertens et al.³⁶⁷. The questionnaire revealed a very high satisfaction from all the patients before and after the treatment. However, some patients complained when chipping or fractures occurred. This aspect is consistent with a study in which the effect of a prosthesis's complication was evaluated over the patient's satisfaction. It was reported that patients experiencing complications with the prosthesis reported a lower satisfaction compared to the ones who did not experienced of any such complications⁴⁶⁵. As reported in **Study III** (Figure 30) the difference in satisfaction before and after the treatment was high compared to the ones reported in the follow-up visits where there was a tendency towards an increase in score among the population.

A more elaborated questionnaire was used in **Study IV**. Even in this study, the patient's perception was statistically higher before and after the treatment, probably related to the good stability of the prosthesis.

Oh et al.³⁶¹ confirmed that OHRQoL improved similarly for FCDs and for IODs compared to CD. The results in **Study IV** were compared with those obtained in other studies with a similar design. Pozzi et al.⁴⁶⁶ reported, in a 1-year prospective study where patients were treated with a four-implant mandibular IOD, a significant improvement in the quality of life in all the patients using an analogue OHIP questionnaire. Kouppala and Raustia in 2015, found excellent OHIP-14 results after treatment with full-arch maxillary restorations⁴⁶⁷.

This finding supports the hypothesis that stable prostheses facilitate lower impairment of patients' quality of life⁴⁶⁸. The importance of the patient-centred outcomes when choosing a treatment option must be underlined. However, the influence of the subjective patient's requests and clinician's influence on a specific treatment, has to be carefully balanced to achieve a more objective and effective treatment outcome.

Technical and biological complications. (Study II-III-IV)

The long-term performance of implant-supported reconstructions is difficult to predict and analyse, and technical and biological complications are major considerations since they are always present^{31,178,250,296,298-300}.

According to a study based on 2.666 patients' files registered by the Swedish Social Insurance Agency (SSIA), 7.6% of patients that experienced implant loss, and 14.5 % presented moderate or severe peri-implantitis after 9 years of follow-up^{288,289}. After 5.3 years of service, 24.8% of patients reported technical complications, and more than 50% had experienced a complication more than once. From the same SSIA register, 31% out of 3827 patients interviewed, reported an implant-related complication⁴⁶⁹. This potentially effects on the supplementary costs of the maintenance as well as an impact on the patient's satisfaction^{169,282,470}.

The majority of complications were counted in **Study III** and the most registered were related to the chipping or fracture of the veneering materials. The risk of complications increased with the increase in suprastructure size²⁸². In contrast with **Study II** and **Study IV**, where each trial had one chipping, in **Study III** chipping and fractures were observed in 12 patients (21.4%) in the first year and 13 patients (24.5%) in the following 2 years (Table 25).

This problem represents a very common complication among patients with FCPs and may appear at any time as a consequence of the fatigue phenomenon typical of any materials following the mechanical failure laws.

In 2003, Gothberg et al.²⁸⁴ reported, in a retrospective study, the complications of 75 patients edentulous in at least one jaw (23% treated in the maxilla and 77% in the mandible) at 3-year follow-ups. The most-reported complications were the fracture of the resin dentition, which was present in 17 out of 75 patients (22.6%).

In 76 consecutively treated maxillary edentulism patients followed for 15 years, Jemt & Johansson⁴⁷¹ reported that the prevalent complication was the rupture of the resin veneers and the wearing of the dentition. Seventy-three fractures were reported in the first 5 years, 71 fractures between 5-10 years and 14 fractures between 11-15 years in 68, 50 and 32 patients, respectively. After 10 years

of service, the authors applied new veneers in four patients due to severe wearing, and in 10 patients an extensively worn dentition was seen. Jemt had already highlighted the same instability of the acrylic matrix in previous publications^{56,472}. Fractures of the resin veneers were observed in different studies by other authors^{81,282,430,473,474}.

Prostheses complication rates seem to be higher for metal-resin restorations, like those reported in **Study III**, compared to all-ceramic and metal-ceramic ones (**Study II**) (Table 3)^{300,475}.

Possible explanations of these high rates of fracture of the veneered teeth reported in **Study III** are as follows:

(i) Laboratory processes during framework production resulting in an improper thickness of the resin material or an under-dimensioned design of the milled framework could transfer unpaired stress between the resin matrix and the core of the suprastructure, resulting in a detachment or fracture of the veneering teeth. According to the original protocols² the framework was conceived and cast with a bulky structure to compensate for the stress distribution during function. This framework design, intended to prevent resin crack, consisted of an Au-alloy throughout the lingual and pontic sides leaving space for final resin application, for cosmetic purposes, in the facial and occlusal areas. However, variations from its original description were proposed to the framework project for two main reasons. The first was the amount of gold used and the associated costs, and the second was related to biomechanical complications due to the heavy bulk of the material used, which transferred unpaired strain and stress to the implant components and the bone. Due to these two reported motives, frameworks began to be manufactured with reduced dimensions in different proposed designs²¹³. With this modification, FCDs had less implant-related component fractures, but an increased fracture rates of the veneering material⁵⁷; some frameworks fractured, especially in the cantilever portion⁴. In our study, it is possible that some frameworks had reduced dimensions that may have enhanced fractures of the veneered teeth^{229,230}.

(ii) A second possible explanation is that the vast majority of the fractures occurred in correspondence with the screw access holes where the framework is, in some cases, extremely under-dimensioned, representing the weakest point of veneering fracture²⁸⁴.

(iii) A third possible reason for the high rates of fracture of the veneered teeth is related to the jaw. The maxilla presents with different biomechanisms with more rehabilitation challenges than similar metalacrylic FPDs in the lower jaw. Several clinical studies have reported that the number of fractures of the veneered teeth in the maxilla are higher compared to in the mandible FCPs. In a retrospective study where 50 edentulous arches were evaluated, 22% of the complications were related to the fracture of the acrylic resin teeth. Moreover, the FCD in the maxilla requires more time for supplementary maintenance⁴⁷⁶.

In 1991, Jemt⁵⁶ reported data on 391 implant-supported FCPs in both jaws after 1 year of function and 14% of the maxillary prostheses presented a fracture of the acrylic teeth after function, while only 1% of the patients reported fracture in the mandible⁵⁶. In a clinical study on prosthodontic complications, where 16 implant centres participated and 600 consecutive patients were treated, it was reported that 60% of complications was related to the acrylic resin matrix with a higher frequency in the upper jaw (34%) than in the lower jaw (24%)²⁸³. Bozini et al.¹³ reported in a metanalysis that the comparison between the fracture in the mandible or the maxilla cannot be analysed.

Ultimately, it has to be reported that a feasible incorrect jaw relation during the prosthetic steps may have enhanced prosthetic complications^{477,478}.

In most cases, veneering material fractures are reversible complications that can be solved with the restoration of the existing prostheses and stabilisation of the occlusion. However, they should be taken into consideration because they affect the overall costs of the treatment for the dental clinic and patients' satisfaction with the treatment^{16,475}.

In **Study III**, the incidence of prosthetic complications was similar between the two groups, with the number of implants having no impact. Interestingly, 11 (47.9%) of patients with chipping or prosthetic tooth fractures presented with an implant supporting FCP as an antagonist, indicating a possible lack of proprioception during jaw function.

The occurrence of complications in **Study III** was not correlated with the extension of the cantilever. Similar findings were reported in a 4-year retrospective study, where the length of cantilevers, in

FDC with Ti framework, was investigated as a possible cause of complications²³⁰.

These possible explanations are confirmed by the findings in **Study IV**, where only one chipping was reported after a 2-year follow-up. It has to be reported that in **Study IV**, the two structures (mesostructure and suprastructure) presented a bulky framework design. Moreover, the retention of the suprastructure on the mesostructure was facilitated by a conometric design that did not require screw access holes.

Similar findings were reported in a 2-year controlled clinical study where the prosthetic maintenance service was evaluated in edentulous patients in the maxilla restored with an IOD or an FCP. The framework was milled in titanium with CAD-CAM technology (Procera® System, Nobel Biocare Services AG, Zürich-Flughafen, Switzerland). After 2 years of function 8 (61.5%) out 13 patients with an FCD presented teeth fracture while no fracture occurred in the 12 patients treated with IOD²⁰³.

The different design of the framework in **Study IV** had a positive impact on the success rate of the prostheses during function compared to **Study III**. Moreover, the retention of the suprastructure on the mesostructure was facilitated by a conometric design that did not require screw access holes. It should be noted that, in **Study IV**, a rigid anchorage system, with a bulky framework design, provided a very stable condition. This was corroborated by a few studies, that analysed the rigid retention system for an IOD and it was described that rigid framework design reduces complication rates^{466,479-481}. In **Study IV**, the counterpart was milled with the mesostructure; this was different from the standard casting procedure as reported by the other authors^{466,479-481}. This rigidity of the milled suprastructure and the mesostructure permitted the use of long cantilevers and treatment of patients with extensive bone resorption (Figure 15).

Considering the prostheses, in **Study III** the plaque was visible on 27 prostheses at 1 year and 33 prostheses at 3 years (Table 25). This is related to the difficulty patients face in the maintenance of FCDs compared to IODs as reported in another clinical trial where patients were treated with IODs and FCDs. The latter group of patients reported more difficulties with maintenance³⁶⁸.

Very few technical complications occurred at the components of the implant.

In **Study III**, four complications occurred in four patients with a rate of 1.53% at implant level and 7.55% at the patient level while, in **Study IV**, 2 prosthetic screws loosened in one patient (Table 26).

These results differ from what has been reported in previous systematic reviews where the incidence of bridge screw loosening and fracture was higher. Moreover, framework fractures were reported to be between 8.8% and 16.9%^{13,15}.

However, a recent systematic review reported a reduction in technical complication rate, mainly related to the new technology and the advanced material used, in contrast with the old convention cast methods (Table 3)²⁹⁹. This statement is in line with the findings of the present thesis; very few technical complications occurred with a CAD-CAM framework in different fixation (**Study II**) or retention type (**Study III-IV**).

In **Study I**, **III** and **IV** the suprastructures were produced with an SM production in, while, in **Study II**, an AM laser melting technique was applied for a final Co-Cr framework melting on the pre-milled connection components with SM (Figure 12). The combination of the high-yield strength of Co-Cr and AM techniques increase the likelihood of restoring partial edentulous zones with implants even with limited space and different shapes⁴⁸². However, Braian et al.²⁴⁰ reported concerns regarding the accuracy of the AM procedures. The accuracy tested was below 50 µm and below 150 µm for the SM and the AM, respectively. The authors stated that when linear and regular geometry, like the framework abutment connection or the IAC are requested, an SM technique has to be chosen and the AM should be used for a customised design of a bridge.

None of the technical complications observed compromised the overall survival of the prostheses, which was 100% in the studies included in this thesis.

In **Study III**, 10 (18.9%) patients and 15 implants (5.74%) reported a biological complication after 3 years of function and only 1 implant was presented with peri-implantitis. In **Study IV** only one implant presented with mucositis (Table 28). This data is corroborated by a controlled clinical trial where milled Ti and prefabricated gold bars were used for IOD restorations. The authors reported the absence

of hyperplasia around the Ti bars probably due to the precision and quality of material used. In contrast, patients treated with prefabricated gold bars reported tissue overgrowth²⁰³.

The biological complications rates reported in **Study III** presented similar data to what has been published in a systematic review¹⁴ where the mean biological complications after 5 years had a rate of 8.5% (5.5-13.2)(Tables 2-3).

In **Study II** and **III**, mucositis was reported if BoP score was ≥ 2 ; however, in **Study IV**, mucositis affected only one implant even if BoP was detected in 22.30% of the sites according to a dichotomous variable.

Limitations of the studies

The studies reported in this thesis presented several limitations.

In **Study I**, the resin embedded blocks may have led to implant displacement during the cycling loading, and thus, reducing the discrepancy may have compensated for the misfit when the load was applied. It could be speculated that implants inserted in a metal cylinder could overcome this issue. Another aspect was related to the number of cycles applied in the fatigue model. The used setup of 1×10^6 cycles, which corresponds to 1.5 years of functional load⁴⁰⁹, may not have been sufficient to trigger a fatigue failure as reported in FEA simulation findings²⁵³.

Another limitation was that implants were placed in a parallel position. It is not improbable that different results would have been obtained if the implants had been placed at a different angulation.

Furthermore, the misfit condition was produced as a horizontal discrepancy, whilst in the clinical environment it may be present in all the three dimensions. It has been reported that angular misfit may be relevant, since it provokes more bone stress compared to only a horizontal or vertical misalignment⁴⁸³.

Another limitation was that the load was transferred vertically to the implants without any kind of lateral force. Different and worse scenarios could be expected in a clinical setting were unfavourable factors, such as the type of occlusion and the patient's parafunctional habits are present. The non-axial directions of the load may aggravate the misfit condition²⁴⁶.

One more limitation that has to be addressed is the simulation. FEA gives an approximation of the solution of a problem and it is more accurate if the model is divided into as many finite elements as possible. However, the mathematical equation and sub-equation to describe each element and their interaction on a built model requires sophisticated software and intense computer hardware. The modern simulations are working on closing the gap between an empirical simulation and reality. The simulation in **Study I** could be implemented in the future by adding a more realistic simulation of the various occlusal scheme patterns.

A limitation of **Studies II, III, and IV** concerns the assessment of perio-markers.

The clinicians involved in these studies did not use a weight-calibrated probe. One of the possible limitations is related to the sensitiveness and the pressure used and the multiple examiners (1 in **Study II**; 3 for **Study III**; 5 in **Study IV**) involved in the clinical studies included in this thesis. The use of calibrated instruments it is reported to be more reliable than at the use of a standard ones^{336,337,484,485}.

In **Study II** one limitation concerns the implant position almost placed straight with a low angular deviation among the implants. A number of different scenarios could be expected with tilted implants.

A further limitation could be related to the different material composition present in the supra-crestal compartment between the IL (Co-Cr) and the AL (Ti) groups. A Ti-metal framework in the IL group may have been more appropriate for the design of the study, limiting possible bias.

Another limitation of **Study II** is the short follow-up period. However, the data published in this study represent interim results of a 5-years clinical trial.

In **Study III** and **IV**, the bone quantity and quality according to Lekholm and Zarb³⁷⁹ or, eventually, the Cawood and Howell classification⁴⁸⁶ was not assessed. Moreover, the implant stability parameters (ITV and ISQ) were not registered with calibrated instruments as in **Study II**. These aspects might have made it possible to analyse and correlate bone quality and quantity condition with MBL change with time.

The samples in the clinical trials were enrolled according to precise inclusion and exclusion criteria and had to participate in a specific maintenance programme. This may not reflect the actual patient population. In clinical reality, patients often fail in attending precise hygiene visits. The new generation of patients consider implant treatment as a general routine procedure and they do not believe that periodical check-ups by the dentist are crucial for their oral health⁴⁸⁷. Different outcomes may be expected in non-compliant patients.

A limitation of **Study III** is the lack of X-ray analyses between implant placement and base-line. The vast majority of bone resorption is reported to take place during the first year of function^{2,434}, and this evaluation may have explained the role of the temporary complete denture on the MBL in the early stage of healing. Moreover, it has been

reported that 86% of the total bone loss develops during the period between implant placement and definitive prosthetic installation⁴².

Another limitation of this thesis is how patient satisfaction was recorded. In **Study III** and **IV** different questionnaires were used. It is possible that a different questionnaire⁴⁸⁸ would have reported more details in the patient's OHRQoL and satisfaction.

In **Study III** the limited psychometric evaluation used with general questions on the OHRQoL may not have reflected the patient perceptions. This aspect was confirmed by other analyses in which the specific questionnaire failed to investigate the totality of the patient's perception²⁸². However, it has to be noted that the outcome that affected the patient's perception was not the primary concern of the investigation in **Study III**, which mainly focused on the clinical outcomes.

Moreover, the answers to patient satisfaction questions may have been biased because patients knew that they were part of the study. The recorded answers may have indicated a false high satisfaction since patients may have skewed their answers for the research⁴⁸⁷.

Different answers and more realistic scores would be obtained if the patients had been interviewed by someone who was not involved in the study. Patients have not been able to provide their emotional feedback on the rehabilitation freely³⁶⁴.

Finally, a limitation of **Study IV** was the lack of a control group. Randomisation with a tissue retention IOD or an FCD would have given more insights into patients' OHRQoL.

CONCLUSIONS

Based on the studies included in this thesis, the following conclusions can be drawn:

1. The risk of implant cracks in screw-retained IL FPD is low, even with a misfit. However, the dynamic load simulation revealed that a crack might likely to occur when the implant is fully supported by the marginal bone than when there is marginal bone resorption.
2. Screw-retained FPDs presented with low MBL change after one year of service in both IL and AL setups. However, the IL group showed greater bone loss and soft tissue inflammation than the AL group. According to the preliminary 1-year data presented in this thesis, AL retention is recommended for FPDs.
3. Implant-supported restorations, using screw-retained CAD-CAM titanium frameworks for FCD in the maxilla and IOD in both jaws, showed satisfactory MBL changes and soft-tissue health at 3- and 2-year follow-ups, respectively. The use of a maxillary FCDs can be successful whether they are supported by four or six implants. The cost-effective 4-implant configuration can be considered as safe and comparable to the 6-implant distribution for a maxillary FCD.

4. Implant-supported FCDs and IODs are associated with high rates of patient satisfaction, related to aesthetics and mastication function mainly resulting from the high stability of the prostheses. PROMs analysis is important for understanding patient requests and choosing the most appropriate treatment for the rehabilitation of edentulism.
5. The technical and biological complications reported in FPDs, FCDs and IODs were limited. However, a considerable percentage of prosthetic fractures and chippings were reported for FCDs at 1-year and 3-year follow-ups. Clinicians have to be aware that additional visits may be required for maintaining the prosthesis.

FUTURE PERSPECTIVES

Following the digital evolution, which is influencing almost every aspect of human life, the considerable growth of technologies in the dental field has encouraged the continuous introduction of new methods and materials. The development of the CAD-CAM techniques for the manufacturing of dental prosthesis does not allow sufficient time to comprehensively evaluate the effectiveness of such a work-flow process.

Companies are allowed to sell new material with very limited or, in the worst cases, no appropriate scientific support. This thesis focused on the use of metal CAD-CAM framework, which preceded recent introductions like the zirconia-based⁴⁸⁹ and polymer-based veneer materials⁴⁹⁰ used for framework productions as veneering purposes. A current trend is the use of the Zi framework glued to hybrid base abutments and directly fixed at the IL. This has not been adequately investigated yet. Therefore, single, partial and total edentulism is often rehabilitated with a lack of long-term knowledge.

Future prospective studies should address this topic and evaluate these novel materials using the mechanical loading test as performed in **Study I**, and a clinical trial as performed in **Study II**. Moreover, digital simulations and mechanical tests could compare different loading setups with tangential forces.

An interesting area would be to clinically compare metal CAD-CAM and Zi frameworks for IL FPDs and FCDs, in terms of MBL change and complication rates.

On the other hand, a more comprehensive understanding of metal CAD-CAM frameworks examined in the present thesis should be investigated during a longer period. In particular, IL and AL FPD

(Study II), maxillary FCD (Study III) and IOD (Study IV) should be compared at 5-year and, possibly, 10-year follow-ups.

From the surgical perspective, RCTs should compare the number of implants used for immediately loaded rehabilitation in the edentulous maxilla, particularly with digital support for guided surgery and prefabricated prosthesis.

Another interest would be to compare fixed (FCD) and removable (IOD) complete rehabilitations in cross-sectional studies. Such comparisons would be of clinical relevance, particularly when evaluating the patient's perspective. Interviews and questionnaires on the patient's satisfaction and improvement in OHRQoL should be blindly performed by external personnel.

This thesis aimed to provide a scientific background on the performance of screw-retained metal CAD-CAM frameworks. Consideration was given to the incidence of complications, and several speculations were raised. The presence of a misfit, the IL setup, an FCD were addressed as possible risk factors for complications.

However, it must be said that there is still no certainty on ascribing a precise phenomenon to the generation of an implant-prosthetic technical and biological complication. Since the implant rehabilitations are incorporated into a complex masticatory system, a specific complication may be the result of a heterogeneous set of contributing factors.

Therefore, the speculations in this thesis were based on numerical results; they can be considered as a simplification and over-generalisation of a much more complex problem. Hence, the proposed conclusions are just theories.

However, the hypothetic-deductive model, reported in 'Science as Falsification' by Karl Popper⁴⁹¹, noted that theories should be able to be falsified. Consequently, the proposed theories are confirmed when there is no correlation between the absence of the trigger conditions and the related disease.

However, even if the falsifiability theory was not universally accepted, novel methods of investigation in the future may be able to verify these theories.

Having said this, a clinician should learn from his/her errors and experience, and focus on obtaining the scientific facts. Moreover, it is imperative to offer the best care and considerations should be made before placing the patient in a needless and, hence, an untenable position with suboptimal clinical results.

POPULÄRTVETENSKAPLIG SAMMANFATTNING

Allt sedan implantologins intåg har konventionellt framställda, dvs. gjutna underkonstruktioner betraktats som det främsta alternativet vid brokonstruktioner för tandersättningar. Den digitala processteknologins utveckling har introducerat CAD/CAM som ett alternativ med kapacitet att minimera risken för operatörsberoende avvikelser och ge bättre möjlighet till en konstruktion med mer homogen struktur och goda mekaniska egenskaper. CAD/CAM-framställda konstruktioner med flera led, kan dock variera utifrån material, anslutning på distans- eller implantatnivå samt passform mellan konstruktion och distans eller implantat. Emellertid kan de nya materialen som introduceras bidra med andra tekniska och biologiska komplikationer som kan uppstå med tiden.

Övergripande mål med föreliggande avhandlingsarbete var att bidra till förståelse avseende risker för komplikationer med skruvretinerade CAD/CAM-framställda brokonstruktioner.

I Delarbete I (*in vitro*-studie) utvärderades effekten av bristande passform med skruvretinerad konstruktion på implantatnivå via uppkomst av sprickor i implantat med olika benstöd. I Delarbete II rehabiliterades delvis tandlösa patienter med en skruvretinerad metallkeramisk konstruktion i koboltkrom antingen på distans- eller implantatnivå. I Delarbete III behandlades tandlösa patienter i överkäken med antingen fyra eller sex implantat och skruvretinerad titan-akrylkonstruktion. I Delarbete IV behandlades tandlösa

patienter med avtagbara täckproteser retinerade till implantatstödda titanbarer. I delarbete III och IV utvärderades även oral hälsorelaterad livskvalitet.

Kliniskt var förändringen av den marginala bennivån inte signifikant oavsett anslutningsförfarande (Delarbete II), retention (Delarbete III-IV) och materialval (Delarbete II, III och IV). Inga komplikationer registrerades på underkonstruktionerna och hög patienttillfredsställelse uppgavs efter behandling (Delarbete III, IV).

Baserat på de studier som ingår i avhandlingen kan följande slutsatser dras: (i) risken för implantatprickor i skruvretinerad fast protetik på implantatnivå är låg, även vid fall med en sämre passform, (ii) enligt 1-års-uppföljningen i Delarbete II, rekommenderas att skruvretinera på distansnivå för fastsittande implantatprotetik, (iii) det kostnadseffektiva alternativet med fyra implantat för en fastsittande fullbrokonstruktion i överkäken kan betraktas som ett säkert och likvärdigt alternativ till behandling med sex implantat, (iv) implantatstödda fullbrokonstruktioner och implantatretinerade täckproteser är förenade med hög patienttillfredsställelse, relaterat till estetik och tuggfunktion, främst till följd av protesernas goda stabilitet, (v) få tekniska och biologiska komplikationer observerades för implantatprotetik i form av sektionsbroar, fullbroar och täckproteser. Trots allt rapporterades en betydande andel ytfrakturer för fullbroar i överkäken vid 1- och 3-årsuppföljningen. Tandvårdspersonal behöver vara medvetna om att uppföljande besök kan krävas för underhåll av protetiska konstruktioner.

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Figure 35. StudioToia's team: (A) Malmö tour 11-13 March 2017;
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PAPERS I-IV

I

Effect of Misfit at Implant-Level Framework and Supporting Bone on Internal Connection Implants: Mechanical and Finite Element Analysis

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Purpose: To evaluate the effect of misfit at implant-level fixed partial dentures (ILFPDs) and marginal bone support on the generation of implant cracks. **Materials and Methods:** This in vitro study included a mechanical fatigue test and finite element analysis. A mechanical cycling loading test was performed using 16 experimental models, each consisting of two parallel implants subdivided into four groups based on the misfit and the supporting bone condition. The framework, firmly seated at implants, was dynamically loaded vertically with a force of 1,600/160 N and 15 Hz for 1×10^6 cycles. Optical microscope, scanning electron microscope (SEM), and computed tomography three-dimensional (CT-3D) analyses were performed to detect impairments. Finite element models, representing the setups in the mechanical fatigue test, were used to represent the fatigue life. **Results:** None of the mechanical components presented distortion or fracture at the macroscopic level during the test. In a microscopy evaluation, the fatigue test revealed scratches visible in the inner part of the conical portion of the implants regardless of the groups. SEM and CT-3D analysis revealed one implant from the misfit/no bone loss group with a microfracture in the inner part of the conical interface. The simulated effective stress levels in the coronal body were higher in the misfit groups compared with the no misfit groups. The misfit groups presented effective stress levels, above 375 MPa, that penetrated the entire wall thickness. The no bone loss group presented an effective stress level above 375 MPa along its axial direction. In the no misfit group, the area presenting effective stress levels above 375 MPa in the conical connection was larger for the bone loss group compared with the no bone loss group. **Conclusion:** This study confirmed that implant fracture is an unlikely adverse event. A clear pattern of effective distribution greater than fatigue limit stresses could be noticed when the misfit was present. The dynamic load simulation demonstrated that the crack is more likely to occur when implants are fully supported by marginal bone compared with a bone loss scenario. Within the limitations of this study, it is speculated that marginal bone loss might follow the appearance of an undetected crack. Further research is needed to develop safe clinical protocols with regard to ILFPD. *INT J ORAL MAXILLOFAC IMPLANTS* 2019;34:320–328. doi: 10.11607/jomi.6965

Keywords: CAD/CAM, finite element analysis, implant fracture, implant level, misfit

The use of implant-supported fixed prosthetic rehabilitation for partial edentulism is supported

by robust evidence on long-term success rates with a small amount of marginal bone resorption.^{1–3} Although high survival rates of fixed partial dentures (FPDs) have been reported, the incidence of biologic and technical complications is nevertheless relevant to discuss. In a meta-analysis by Pjetursson et al,⁴ the patient-centered esteemed 5-year FPD complication rate was 38.7%.

To prevent technical complications in screw-retained constructions, a passive fit between the components is advocated.⁵ A perfect fit was defined as simultaneous contact of all the fitting surfaces with the absence of strain before load application.^{6,7} However, this represents an ideal condition, and it is hardly reproducible in the clinical reality. The generation of misfits between the components is inevitable throughout the prosthetic procedures, starting from the impression to the construction delivery.⁸

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Different techniques have been suggested to minimize the inaccuracy in the production of the framework such as splinted impressions,^{9,10} low fusing metal casts,¹¹ and computer-aided design/computer-aided manufacturing (CAD/CAM) technology.^{12–14}

Nevertheless, when the fit is inadequate, uneven stresses and strains are introduced in the interface between the framework and implant. This condition has been indicated to be one of the causing factors for mechanical complications, such as screw/abutment loosening or fractures, framework fracture, and, in the worst scenarios, implant fracture and implant loss.¹⁵

It is unclear whether an implant fracture is a consequence or a cause of marginal bone loss.^{16,17} Metal cracks in the implant may be caused by unfavorable bending stresses when excessive resorption of the supporting bone has occurred.¹⁸ On the other hand, a preexisting undetected crack might be the cause of marginal bone loss.^{19,20} In fact, the stress distribution on the implant body when misfit is applied to implants with different supporting bone levels is unknown.

Thus, the present study aimed to evaluate the effects of misfit at implant-level fixed partial dentures (ILFPDs) and supporting bone level on the generation of implant cracks with a coupled method of a mechanical test and finite element analysis (FEA).

MATERIALS AND METHODS

Mechanical Fatigue Test

A mechanical cycling loading test was performed using an experimental model consisting of two parallel implants with a diameter of 3.5 mm and a length of 11 mm (Astra Tech Implant System Osseospeed TX, Dentsply Sirona Implants). The implants were embedded in epoxy resin cylinder with a diameter of 10 mm and a length of 13 mm and firmly seated in an aluminum block (60 × 60 × 40 mm).

Two metal blocks were manufactured to mimic the perfect fit and the misfit condition, defined as the discrepancy between the implant longitudinal axis and the restorative longitudinal axis,²¹ as follows:

- *No misfit*: The distance between the center of the two implants was 35.0 mm.
- *Misfit*: The distance between the center of the two implants was 35.2 mm.

Moreover, to detect the effect of supporting bone level, implants were placed with different embedding depths:

- *No bone loss*: The implant shoulder was placed at 0.0 ± 0.5 mm above the surface of the epoxy resin (nominal level).
- *Bone loss*: The implant shoulder was placed at 3.0 ± 0.5 mm above the nominal level according to ISO std. 14801:2007, simulating the worst bone loss scenario (Fig 1).

Sixteen computer-numeric-controlled (CNC)-milled Titanium Bridge Type rigid frameworks ($42 \times 10 \times 7.5$ mm) (Atlantis Superstructures, Dentsply Sirona) were fabricated from the same file with a distance between the center of the two implants of 35 mm. The accuracy of the frameworks is granted by CNC-milling manufacturing, which was demonstrated to have small variability and high precision with an amount of error of less than $10 \mu\text{m}$.^{22,23}

The total length of the conical connection was 2 mm, and the depth of the framework into the implant was 1.2 mm. The frameworks, free from antirotational interlocking, were screwed with a torque of 20 Ncm into the implants. Radiographs were taken after the final position of the framework to check the presence of misfit.

Experimental models ($n = 16$) were subdivided into four groups based on the misfit condition and the supporting bone condition, as shown in Fig 1.

The framework was externally dynamically loaded vertically in the center using a loading machine (Electropuls E3000, Instron) with a force of 160 to 1,600 N at 15 Hz for 1×10^6 cycles. The rigidity of the framework minimizes unfavorable bar deformation, inducing an equal vertical load and negligible bending moment to the implant-abutment interface. Therefore, the expected dynamic load on each implant varied between 80 and 800 N. After loading, the embedded implants were removed from the metal block and examined through an optical microscope with a $\times 50$ magnification lens (ZEISS Stemi 2000-C Stereo Microscope).

Afterward, the samples were investigated using a scanning electron microscope (SEM) (Hitachi TM3000, Hitachi). Implants were placed in a tilted fashion into the vacuum camera. Each implant was rotated 60 degrees and analyzed three times to obtain a complete view of the conical inner side.

As a final examination, the samples were analyzed with an industrial computed tomography three-dimensional (CT-3D) X-Ray Measuring System (ZEISS Metrotom 800 CT system). The measurement conditions were set at 95 kV and 80 μA . The primary x-ray beam was filtered by a 0.5-mm-thick aluminum target. Eight hundred fifty high-resolution (scan resolution of $10.17 \mu\text{m}$, voxel dimension) radiographs were collected, by spinning the sample in autofocus mode, in no more than 60 minutes. Special software (Volume

Fig 1 Experimental models subdivided into four groups based on implant vertical position and misfit: (a) misfit/no bone loss, (b) misfit/bone loss, (c) no misfit/no bone loss, and (d) no misfit/bone loss. Arrow represents the direction of the loading.

Fig 2 (a) FEA model simulated for one implant side. (b) Multilinear material properties.

Graphics) was used to reconstruct the two-dimensional (2D) images into a 3D volume.

Finite Element Analysis

To investigate the stress distribution at the implant, finite element models, representing the setups in mechanical fatigue tests, were developed in ANSYS 18.2 (ANSYS).

Taking advantage of the symmetry of the model, only one implant side was simulated (Fig 2a). To capture the mechanical properties of the metallic components, the simulations were performed using multilinear material properties (Fig 2b). This model captures the increase in stress between yield and ultimate strength. In addition, this material model limits the simulated stress to the ultimate stress.²⁴ The interface between the framework and the implant was modeled with a friction coefficient of 0.3.²⁵ To reduce the simulation time, the interface between the framework and the abutment screw was modeled as a frictionless connection, while the interface between the implant and support material was modeled as a bonded one.

The meshes were generated using the ANSYS default settings with a denser mesh size of 0.075 mm in the implant-framework interface. These settings resulted in 0.13×10^6 nodes and 0.08×10^6 elements of the bone loss condition and 0.19×10^6 nodes and 0.12×10^6 elements of the no bone loss condition.

To analyze how the mesh density affected the results, the model that comprised a misfit of 0.2 mm and 0 mm bone loss was modeled with an increased mesh of 0.05 mm and with a reduced mesh of 0.1 mm at the implant-framework interface.

Tightening of the framework was simplified in the FEA model to only include a screw preload of 250 N and neglecting any shear forces arising due to screw torquing.²⁶ This simplification does not suppose to affect the results in the coronal part of the implant. To replicate the experimental setup, the preload was applied first; thereafter, a maximum load of 800 N was applied on the implant at the implant-framework interface.

The stress levels were analyzed by the mean von Mises stress criterion. The alternating stress range (σ_r) was defined as the difference in von Mises stress

Fig 3 Stress-life diagram (S-N) of titanium Gr 4 with a UTS of 820 MPa, reflecting the mechanical properties of the implant used in the in vitro fatigue test. The S-N curve of Ti Gr 4 with UTS of 820 MPa (red line) was derived from an offset of the S-N curve of Ti Gr 4 with a UTS of 470 MPa (green).²⁸

Fig 4 SEM analysis revealed one implant from the misfit/no bone loss group with a microfracture in the inner part of the conical interface ([a] $\times 150$ and [b] $\times 1.80K$ magnification).

between 800 N (maximum stress level $\sigma_{\max}$) and 80 N (minimum stress level $\sigma_{\min}$):

$$\sigma_r = \sigma_{\max} - \sigma_{\min}$$

The alternating stress amplitude (σ_a) is defined as:

$$\sigma_a = \sigma_r / 2.$$

The mean stress level (σ_m) is defined as:

$$\sigma_m = (\sigma_{\max} + \sigma_{\min}) / 2.$$

In this simulation, the modified Goodman theory was used to assess fatigue life.²⁴

The mean stress correction by Goodman results in an effective fully reversed stress amplitude (σ_{er}) that can be used to compare with an existing stress life diagram (S-N) of fully reversed load ($R = -1$) of titanium Gr 4:

$$\sigma_{er} = \sigma_a \times \left(1 - \frac{\sigma_m}{\sigma_u}\right)$$

where σ_u is the ultimate tensile strength (UTS) of the material.²⁷

The effective fully reversed stress amplitude σ_{er} found in this simulation was compared with a stress-life diagram (S-N) of titanium Gr 4 with a UTS of 820 MPa, reflecting the mechanical properties of the implant used in the in vitro fatigue test. The S-N curve of Ti Gr 4 with UTS of 820 MPa used in this study was

derived from an offset of the S-N curve of Ti Gr 4 with a UTS of 470 MPa presented by Chandran (Fig 3).²⁸ The offset was calculated as the ratio between UTS 820 and UTS 470.

RESULTS

Mechanical Fatigue Test

Prior to torquing the framework to the implant, a misfit was clearly visible in both misfit groups and also detectable on radiographic images after the final torque fixation.

None of the mechanical components presented distortion or fracture at the macroscopic level during the test. After the test, no microfractures of the prosthetic screws were detected.

The microscopy evaluation demonstrated some scratches visible in the inner part of the conical portion of the implants regardless of the groups. SEM and CT-3D analysis revealed one implant out of eight from the misfit/no bone loss group with a microfracture in the inner part of the conical interface (Figs 4 and 5). Scratches, wear, minor damages, and titanium debris were a common finding at the interface of the majority of the implants regardless of the groups in SEM analysis.

Finite Element Analysis

Decreasing the mesh did not dramatically affect the von Mises stress level at the circumferential opening at the coronal portion of the implant as presented in Fig 6. Therefore, to reduce simulation time, a mesh size

Fig 5 (Above) Computed tomography 3D (CT-3D) x-ray analysis revealed one implant from the misfit/no bone loss group with a microfracture in the inner part of the conical interface.

Fig 6 (Left) Von Mises stress level at the circumferential opening, starting from the misfit contact side, at the coronal portion of the implant of three different mesh sizes (green 0.05 mm, red 0.075 mm, black 0.1 mm).

Fig 7 Simulated effective stress levels in misfit groups. (a) Misfit group, 0 mm bone loss, external side. (b) Misfit group, 0 mm bone loss, internal side. (c) Misfit group, 3 mm bone loss, external side. (d) Misfit group, 3 mm bone loss, internal side. (e) No-misfit group, 0 mm bone loss, external side. (f) No-misfit group, 0 mm bone loss, internal side. (g) No-misfit group, 3 mm bone loss, external side. (h) No-misfit group, 3 mm bone loss, internal side.

of 0.075 mm in the implant-framework interface was used for all other simulations.

The simulated effective stress levels in the coronal body were higher in the misfit groups compared with the no misfit groups.

Effective stress lower than 375 MPa represents a lifetime ($N > 1 \times 10^6$ cycles) (Fig 3). The misfit groups presented effective stress levels, above 375 MPa, that penetrated the entire wall thickness. The no bone loss group presented an effective stress level above

375 MPa along its axial direction (Figs 7a to 7h). In the no misfit group, the area presenting effective stress levels above 375 MPa in the conical connection was larger for the bone loss group compared with the no bone loss group (Fig 7).

DISCUSSION

In this study, the effect of misfit at screw-retained CNC-milled frameworks when connected at the implant level was investigated with a coupled method of an in vitro fatigue model and FEA.

It has been reported that conical implant-abutment connections for screw-retained restorations exhibit better continuity in yield forces,^{29–31} and possess high rigidity³² with low risk for leakage compared with external or internal butt joints.^{33,34}

Arguably, internal conical connection may present mechanical disadvantages because of the reduced coronal wall thickness, having a decreased bearing capacity.^{18,35}

To rehabilitate partial edentulism with screw-retained FPDs, the placement of a multiunit abutment between the implant and the framework has previously been recommended.³⁶ Such an abutment would protect the implant from overload by compensating the misfit between the components.³⁷

Implant-level restorations have been developed by Lewis et al³⁸ to treat patients with limited intraoral vertical space. Few studies investigated the clinical outcome of implant-level reconstructions,³⁹ especially in conical connection implants.^{40,41} Some authors suggested that ILFPDs are one of the most challenging situations; yet, they are frequently used in daily practice to reduce cost and improve esthetics.^{42,43} This type of reconstruction requires highly accurate prosthetic procedures in order to not induce critical stresses in the implant-framework interface.⁴⁴ Unfavorable stress levels and metal fatigue increase the risk of mechanical complications.^{20,45}

In the present study, a cycling load model was developed so that repeated stresses predisposed the implants to fail under fatigue. This model was considered to be a more clinically relevant approach than static fracture tests.⁴⁶ The magnitude of load was chosen in accordance with the maximum occlusal force recorded in humans with an implant-supported reconstruction in the posterior area of the jaw.^{47,48}

A 200- μ m misfit between the implants and the framework was introduced. In a recent review, such an amount of discrepancy was considered as a very poor fit and not clinically acceptable.⁷ However, some authors reported that a misfit of more than 200 μ m has minor influence on clinical outcomes.^{49,50}

It has been reported that a kind of bone adaptation occurs when a framework is connected to an implant, and peri-implant bone stress will increase with a certain degree of remodeling. In vitro, in vivo, and clinical studies demonstrate that implant displacement occurs, reducing the total amount of misfit and total compensation of approximately 20 μ m.¹³ Still, this potential displacement is more pronounced if the connection between the framework and implant is fixed in the early phase of healing. Further, no study evaluated if the effect of misfit on an implant-level setup in a conical connection implant has a mechanical or biologic impact.¹³

The results from the fatigue loading model revealed that only one implant out of 32 presented signs of material failure. One crack (Fig 4) was detected in the SEM analysis at the inner surface of one implant out of eight in the misfit/no bone loss group. This finding was also confirmed in the CT-3D analysis, where the crack engaged the implant wall (Fig 5).

Repetitive applied force generating stress levels below yield might result in material failure as a result of the load cycles. Goodman's mean correction theory was used to evaluate the fatigue life of the implant. This theory calculates an effective stress, based on the stress amplitude and mean stress, that could be compared to experimental S-N curves of fully reversed load; ie, the mean stress is 0.

Generally, there are different theories used to analyze the influence of a fluctuating stress. Goodman's theory has a conservative approach and underestimates the fatigue life, and the choice was made to incorporate a potential error in the model setup.²⁴ This might explain why there was only one sample of the physical test that resulted in a crack while the FEA presented a lifetime less than 1×10^6 cycles above 375 MPa. The objective was to identify if there is an increased risk of fatigue in the implant with increased misfit with two different supports during cyclic load. Therefore, all four groups were simulated using the same FEA setup. Hence, this simulation neglects fatigue life dependencies such as surface treatment and stress concentration factors (ie, notch effects). However, these factors are assumed to provide similar dependencies of all four models.

The FEA performed in this study revealed a clear pattern of effective stress concentration along all implant-framework connections. This finding is in accordance with a previous study,²¹ in which the effect of misfit at the connection between the implant and two-unit ILFPD was simulated.

The fatigue limit, at 1×10^6 cycles, of Ti Gr 4 has been reported to be approximately 50% of UTS.⁵¹ This is in the same range used in this study (Fig 3), indicating that the offset approach of the fatigue data presented

by Chandran seems reasonable.²⁸ Visually, the simulated effective stress is presented in Fig 7, where the green color represents the fatigue limit of titanium at 1×10^6 cycles. In the misfit/no bone loss group, a vertical region of effective stresses above the fatigue limit was presented. The high location of these high stresses seems to penetrate through the wall thickness that might initiate a fatigue crack (Fig 7a). These high simulated effective stresses of the misfit/no bone loss group coincide with the location of the crack detected at the SEM and at the CT-3D (Figs 4 and 5).

The bone loss groups presented areas of high simulated effective stresses that seemed not to penetrate through the wall thickness to the same extent as found in the misfit/no bone loss group.

From the present FEA findings, preserved supporting bone level (no bone loss) seemed to increase the risk of vertical fracture compared with the bone loss groups, when there is a misfit. One explanation might be that, in the absence of full support (bone loss), the implant more easily adjusts to the final position, hence reducing the simulated effective stress. This might explain why no cracks were found in the samples of the bone loss groups after the fatigue test. In addition, the discrepancy between results from the mechanical test and FEA is not totally surprising since it was previously observed that fatigue tests may fail to identify the crack initiation site.⁵² Furthermore, the screw preload maintained a minimum force of 250 N in the conical portion of the implant that decreased the alternating stress. This could explain why only one sample presented a crack despite the high load of 800 N.

Arguably, another factor that could have influenced the in vitro results was the possibility to maintain the discrepancy during the cycling loading. It could be speculated that the resin embedded blocks inserted in the metal block could have compensated the misfit when the load was applied.

Moreover, the number of cycles applied in the fatigue model, which corresponded to 1.5 years of functional load,⁴⁶ might not have been sufficient to trigger a fatigue failure.²⁸

A limited incidence of implant fracture has been reported in different systematic reviews to occur in less than 1% of all implants during a 5-year period.^{18,53,54} Nonetheless, this evidence is likely to be underestimated,¹⁹ and it is reported to appear more frequently in a multiunit partial restoration than in a full-arch replacement.¹⁵

It must be said that, among the limitations of this experimental setup, the implants were placed in a parallel position. Different results can be expected in terms of fractures when an angulation between the implants is present. Furthermore, the misfit condition

was generated only as a horizontal interimplant discrepancy, but in the clinical reality, it may occur in all three dimensions. Such a condition of angular misfit may be relevant, since it was observed that it provokes more bone stress in comparison to only horizontal and vertical ones.⁵⁵ Moreover, aggravating factors may include the type of occlusion and the patient's parafunctional habits, which may persist in long-term time intervals and repetitive stress concentrations, above the yield limit, and could provoke minor, moderate, or major mechanical failures such as implant fracture.¹⁵

This in vitro experiment seems to confirm the clinical evidence that implant fracture is an uncommon adverse event, even when a large framework misfit is present. However, the location of high-stress areas highlighted in the computational model must be seriously considered by the clinician when a multiunit ILFPD is chosen as the treatment plan.

Clinicians must follow a precise prosthetic protocol to reduce the potential degree of misfit, such as splinting impression, and use methods to validate the master model.⁹⁻¹² Moreover, if unfavorable clinical conditions such as parafunctional habits and/or an interimplant angulation that exceeds the conical total axis deviation persist, an abutment-level connection should be recommended instead of implant-level ones.³³

The present findings suggest that implant fractures are more likely to occur when implants are fully supported by marginal bone, hence supporting the claim that cracks appear before bone loss. Therefore, it might be speculated that a secondary bacterial contamination of undetected fractured surfaces would cause a rapid bone breakdown.

Future clinical studies should evaluate the incidence of implant fracture comparing implant-level restorations with different setups, including abutment-level restoration.

CONCLUSIONS

With the limitation of this setup, this study confirmed that implant fracture is an unlikely/adverse event. A clear pattern of effective stress distribution greater than fatigue limit stresses could be noticed when the misfit was present. The dynamic load simulation demonstrated that the crack is more likely to occur when implants are fully supported by marginal bone, compared with a bone loss scenario. Within the limitations of this study, it is speculated that marginal bone loss might follow the appearance of an undetected crack. Further research is needed to develop safe clinical protocols with regard to ILFPD.

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II

ORIGINAL ARTICLE

Implant vs abutment level connection in implant supported screw-retained fixed partial dentures with cobalt-chrome framework: 1-year interim results of a randomized clinical study

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Abstract

Background: Screw-retained fixed partial dentures (FPD) have shown a lower incidence of biologic complications and an easier retrievability compared with cemented FPD.

Purpose: To compare the marginal bone loss at conical connection implant restored with a screw retained cobalt-chrome FPD in an implant-level (IL) or an abutment-level (AL) setup.

Materials and Methods: Patients with at least two adjacent missing teeth were randomly allocated to be restored with IL or AL FPD. Periapical radiographs and clinical examination were taken at implant placement, prosthetic connection, 6 and 12 months to evaluate marginal bone loss (MBL), and soft tissue conditions. Complications were used to calculate prognostic indexes.

Results: Fifty patients were treated with 50 FPD supported by 119 implants. The difference of MBL between the IL and AL groups was statistically significant ($P = 0.003$). At 1 year, MBL was 0.086 ± 0.313 mm and 0.005 ± 0.222 mm in the IL and AL groups, respectively. The presence of BoP increased with time in IL, whereas it decreased in AL group ($P < 0.001$). A minor complication was encountered in one FPD.

Conclusions: A low grade of MBL was present after 1 year. IL showed greater amount of MBL and soft tissue inflammation indexes than AL. In FPD, AL may be a safer procedure than IL setup in order to preserve a healthy periimplant tissue.

KEYWORDS

Co-Cr, dental implant, fixed partial dentures, implant level connection, marginal bone loss

1 | INTRODUCTION

Long-term survival rates and high patient satisfaction have been observed with implant-supported fixed partial dentures (FPD).^{1,2} Compared with cemented solutions, screw-retained FPD have shown a lower incidence of biologic complications and an easier retrievability.³ According to the original protocol,⁴ the interposition of an abutment between the implants and the framework was recommended. This abutment-level (AL) setup would protect the implant from overload and counterbalance potential misfit between framework and the implants.⁵

Nevertheless, in the clinical reality, a framework is often screwed directly to the implants, avoiding the use of a screw-retained

abutment.⁶ This implant-level (IL) setup is often used in cases due to limited vertical spaces and to reduce costs.⁷ Very few mechanical complications were reported in a 5-year prospective multicentre study in which total and partial fixed dentures were directly screwed to the implants.⁸ However, IL restoration may be more susceptible to inaccuracy between the components. The presence of misfit, although inevitable during the prosthetic procedures,⁹ could generate uneven stresses and strains between the framework and implant, which may cause relevant complications, such as screw fracture, framework fracture, implant fracture, marginal bone loss (MBL), and implant loss.¹⁰ In contrast to AL setup, the accuracy of IL framework seems to be negatively affected by implant disparallelism, when using systems with

internal connection.¹¹ Thus, it was advocated not to have excessive disparallelism between the implants in this setup.¹²

Moreover, to allow the insertion and a passive engagement of an IL FPD, the framework is often manufactured without antirotational interlocking indexes. As a consequence, the length of implant-framework interface is reduced both in conical as well as in internal hexagon connection designs. This modified configuration may prevent the benefits of the original internal implant design. It was previously reported that shortened implant-framework interface may introduce higher risk of microgaps between implant and FPD, which may influence both the mechanical engagement and the biological stability of the soft and hard periimplant tissues.¹³

Based on the current literature, the IL setup has an unclear clinical recommendation,¹⁴ and the choice between AL and IL setups is debatable.⁶

A 1-year prospective clinical study by Gothberg et al.,¹⁵ used implants with external hexagonal connection. They observed greater marginal bone resorption on IL restorations compared with an AL setup.

Compared to external or internal butt joints, conical implant-abutment connections exhibit better continuity in yield forces^{16,17} and possess high rigidity with low risk for leakage.^{18,19} Nevertheless, internal conical connection may present mechanical disadvantages because of the reduced coronal wall thickness of the implant and may therefore have a decreased bearing capacity.^{20,21} However, there is no clinical evidence comparing IL and AL setups for screw-retained restoration in implants with conical connection.

The primary objective of this preliminary report of a 5-year study was to present results of MBL at implants with conical connection restored with a screw-retained cobalt-chrome (Co-Cr) FPD in an IL or AL setup after 1 year of follow-up. Clinical parameters, such as soft tissue status, mechanical, technical, and biological complications, were evaluated as secondary objectives. The null hypothesis of the study was that there is no difference in soft and hard tissue changes as well as no difference in prosthetic complications between the two groups.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective investigation was performed in one clinical center affiliated to the Department of Oral and Maxillofacial Surgery and Oral Medicine, Malmö University, Sweden. One (MT) clinician performed all the surgical as well as the prosthetic steps of the treatment, whereas an external examiner, not involved in the study, collected data on the clinical parameters.

The study protocol was approved by the Medical Ethics Committee "Azienda Ospedaliera di circolo", Italy ((VA) number 0001832). The clinical trial was registered at the U.S. National Institutes of Health (Clinicaltrials.gov): NCT02789956. The CONSORT 2010 checklist was used as a guideline to report on the outcomes. The study flowchart is presented in Figure 1.²²

FIGURE 1 Flowchart diagram of the study protocol according to Consort guidelines²²

2.2 | Patient selection

Patients were selected to be included in the study based on the following criteria:

1. Age ≥ 18 years.
2. Willingness to comply with all study requirements and to sign an informed consent.
3. Absence of systemic medical condition: patients had to be ASA-1 or ASA-2.²³
4. Good oral hygiene defined as full mouth plaque score $\leq 25\%$.²⁴
5. Patients with at least two adjacent teeth to replace in any quadrant of the jaws.

Patients were excluded based on the following criteria:

1. Implant-treated patients with bone defects in need of major bone augmentation;
2. Patients with bone defects resulting from tumor resection;
3. Smoking more than 10 cigarettes per day;
4. Severe renal and liver disease;
5. History of radiotherapy in the head and neck region;
6. Chemotherapy at the time of the surgical procedure;
7. Uncontrolled diabetes;
8. Mucosal disease (such as oral lichen planus and epidermolysis bullosa), in the areas to be treated;
9. Noncompliant patients;
10. Situations that the main investigator considered unsuitable for the surgical treatment.

Patients were thoroughly informed about the treatment. The study was conducted in accordance with the Helsinki declaration.

2.3 | Pretreatment

Patient data, medical history, clinical and radiographic examination were recorded.

Periodontal, endodontic, and open caries lesions were treated prior to implant installation. All patients received careful oral hygiene instructions and training in self-performed plaque control measures before the surgery. Orthopantomogram at constant magnification and CT scan exams were carried out.

2.4 | Surgical procedures

Each patient received antibiotic prophylaxis (Amoxicillin 2 g) 1 hour prior to implant placement (IP). A different antibiotic was prescribed for the penicillin-allergic patients. Patients rinsed chlorhexidine 0.2% for 1 minute prior to surgery and local anesthesia was induced. After a crestal incision, a full thickness flap was elevated and 2, 3, or 4 implants (OsseoSpeed EV Astra Tech Implant System, Dentsply Sirona Implants, Mölndal, Sweden) were placed in each patient according to the drilling protocol described by Toia et al.,²⁵ using a two-stage procedure. The implant bone site was classified according to Lekholm and Zarb classification (L&Z)²⁶ and insertion torque value (ITV) was registered using SA-310 W&H Elcomed implant unit (W&H, Burmoos, Austria). Implant spinning during the positioning of the cover screw was registered. The operation was finalized by a primary adaption of

the flaps by means of an accurate suture using absorbable 5-0 suture (Vicryl, Ethicon J&J International, St-Stevens-Woluwe, Belgium) to obtain full periosteal coverage. The patients were instructed to rinse twice daily with chlorhexidine and to have a soft diet for 14 days. Sutures were removed after 2 weeks. The patients were advised to take nonsteroidal antiinflammatory drugs for pain relief at their own discretion.

2.5 | Second-stage surgery and randomization

At the second-stage surgery, 6 weeks after IP, the randomization was performed. Computer randomization block software was used to assign the patients in two groups: one group was prosthetically restored at the AL and the other group at the IL. In the AL group, the cover screws were removed and a screw-retained index-free abutment (Uni Abutment 33° EV Dentsply Sirona Implants, Mölndal, Sweden) was secured using a torque wrench at 25 Ncm. A healing cap (Uni Abutment EV Heal Cap Dentsply Sirona Implants, Mölndal, Sweden) was positioned onto the abutment, and a suture was applied if necessary. In the IL group, the cover screws were replaced with healing abutments (Healing abutments, Heal Design (TM) EV, Dentsply Sirona Implants, Mölndal, Sweden).

2.6 | Prosthetic and technical procedures

Impression was taken, using a customized impression tray and silicone elastomeric dental impression material (Aqualil Ultra, Dentsply-Sirona, Milford, Connecticut), 1 week after the second-stage surgery.

After the master cast was poured, the technician produced both a gypsum index, connecting temporary index-free abutments to validate the model as well as an anatomical wax-up. The index was fixed and its final position checked with a periapical radiograph whereas the wax-up was regulated according to the occlusion. In case the index would break, a new impression was taken, and a new index was produced and checked in the patient's mouth. The master model and the anatomical wax-up were then sent to a milling center (Atlantis suprastructures, Dentsply Sirona Implants, Hasselt, Belgium). The model and the wax-up were scanned, and a cut-back digital superstructure design was produced and uploaded in the software (Atlantis suprastructures viewer, Dentsply Sirona Implants, Hasselt, Belgium) for final review and approval prior to fabrication.²⁷ Framework was produced in Co-Cr with an additive manufacturing process on the milled implant connection interface.²⁸

Four (± 2) weeks after the impression, the definitive screw-retained FPD was installed: baseline timepoint (BL). In the AL group, the screw-retained index-free abutment was secured using a torque wrench at 25 Ncm before seating the framework. The screw hole was closed with polytetrafluoroethylene (PTFE) and composite.²⁹ Each patient received a careful hygiene and motivational instruction after the delivery and was recalled for examination and professional cleaning at 6 months (6M) and 1 year (1Y) follow-up visits.

2.7 | Radiographic parameters

Standardized periapical radiographs were taken after the surgery at IP, BL, 6M, and 1Y with an X-ray apparatus supplied with a long cone and a Rinn Universal Collimator (Dentsply RINN, York, Pennsylvania) (Figure 2).

The digital radiographs were analyzed using a software (IllustratorCS, Adobe Systems, Inc. San Jose, California) on a 24-inch high-resolution screen (iMacApple Inc, Cupertino, California) to measure periimplant MBL. The distance from the mesial and distal interproximal bone to the implant-abutment connection (bevel) was measured to the nearest 0.1 mm, and a mean of these two measurements was calculated for each implant. If the bevel was at or below the margin of the crestal bone, that is, subcrestal, the value was considered zero. The known implant diameter and length were used to calibrate the measurements for any distortions (screen resolution was 1920×1200 pixels).

The radiographs were analyzed at the Department of Radiology, Sahlgrenska Academy, Gothenburg University, Sweden, by one experienced radiologist who did not take part in any of the clinical procedures.

2.8 | Clinical examination

Clinical measurements were performed at BL, 6M, and 1Y. The same examinations performed at BL were conducted at each visit.

Plaque index (PI), probing pocket depth (PPD), bleeding on probing (BoP), and presence of keratinized mucosa (KM) was examined and registered.

PI was scored as 0 (no detection of plaque), 1 (plaque only recognized by running around with a probe the abutment/framework), 2 (visible plaque), 3 (abundance of plaque).

PPD was calculated by measuring the distance in millimeter (approximated to the nearest 0.5 mm) from the periimplant mucosal margin to the bottom of the mucosal pocket, using a periodontal calibrated probe (PCP 15; Hu-Friedy Manufacturing Co, Chicago, Illinois).

The BoP was assessed as "0" (no bleeding), "1" (minute bleeding), and "2" (abundant bleeding).³⁰

Keratinized mucosa (KM) was measured on four implant sites (mesial, buccal, distal, and lingual/palatal) from the gingival margin till the muco-gingival junction. It was assessed as "0" (no KM meaning that the gingival margin was lining mucosa), "1" (partial presence of KM <2 mm) and "2" (complete presence KM >2 mm).

Additionally, the papilla fill was registered mesial and distal at each implant site according to Jemt's classification.³¹

2.9 | Complications

Mechanical, technical, and biological complications were investigated. For mechanical complications following events were registered: implant failure or fracture; abutment and bridge screw mobile mobility or fracture. Technical complications were considered: framework fracture; ceramic layer chipping or fracture. Biological complications were considered: mucositis, fistula, hyperplasia, and perimplantitis. The complications were reported and used to calculate the prognostic indexes.³²

2.10 | Statistical analysis

MBL was set as the primary outcome, and prosthetic and clinical complications (implant failure, fracture of prosthetic components, bacterial plaque accumulation, BoP, PPD) were set as the secondary outcomes. The mean, SD, and percentage were calculated for all variables. The Kolmogorov-Smirnov test was performed to evaluate the normal distribution of the variables, and Levene's test evaluated homoscedasticity. Differences between control and test groups were compared with the student's *t*-test or Mann-Whitney test for continuous variables, depending on the normality. Pearson's chi-squared or Fisher's exact test was used in the analysis of contingency tables of categorical data. Survival analyses were performed. A life table was presented with cumulative survival rate (CSR) of both implants and prostheses, besides Kaplan-Meier analysis. The software used was the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS Inc., Chicago, Illinois). The degree of statistical significance was considered $P < 0.05$.

FIGURE 2 X-rays at each time point in abutment level patient (AL) and in implant level patient (IL). Implant placement (IP), prostheses delivery-base line (BL), six months follow-up (6M), one year follow-up (1Y)

TABLE 1 Summary of the number of implants inserted in each patient and number of the corresponding FPD units

Number of Implants	Patients	FPD units				
		2	3	4	5	6
2	35	20	14	6		
	AL	15	11	4		
3	11	2		1	1	
	AL	9		3	4	1
4	4	3			1	2
	AL	1			1	
Total	50	50	25	14	6	4

Abbreviations: AL, abutment level; IL, implant level.

TABLE 2 Results for ITV(Ncm) in jaws, bone quality, and drilling protocol

	N	ITV	P-value
		Mean (SD; min-max)	
Jaw			<0.001
Mandible	66	31.7 (9.8;12-58)	
Maxilla	53	20.1 (6.6; 9-33)	
Bone quality (L&Z)			<0.001
1	6	50.7 (4.2;47-58)	
2	49	32.0 (6.4;21-48)	
3	47	22.3 (5.9;11-33)	
4	17	13.9 (3.8;9-25)	
Drilling protocol			<0.001
S	31	21.2 (7.9;10-48)	
S-A	17	20.3 (6.0;10-32)	
S-B	18	29.3 (9.5;9-45)	
S-X-B	53	30.7 (10.6;11-58)	
Total	119	26.5 (10.2;9-58)	

Abbreviations: L&Z, Lekholm & Zarb classification²⁶; Min, Minimum; Max, Maximum; N, Frequency; S, S-A, S-B, S-X-B (Drilling protocol: S = step drill; A = cortical drill; B = cortical drill; X = body drill)²⁵.

3 | RESULTS

3.1 | Patient demographics

Fifty patients (21 males, 4 smokers), with a mean age of 58.9 years (SD 12.1, range 35.6-93.5) were treated with 50 screw-retained FPD supported by 119 implants between January 2015 and October 2016. The IL group included 25 patients (8 males, 3 smokers), with a mean age of 57.3 years (SD 9.9, range 41.4-73.2) and were treated with 58 implants. The AL group consisted of 25 patients (13 males,

1 smoker), mean age 65 years (SD 13.9, range 35.6-93.5) were treated with 61 implants. The summary of the number of implants in each patient and number of FPD units is reported in Table 1.

Sixty-six implants were placed in the mandible and 53 in the maxilla. In the AL group, the abutments were divided in to three lengths resulting in: 21 abutments of 1 mm, 33 of 2 mm and 7 of 3 mm.

3.2 | Surgery specifications

ITV resulted in a mean of 26.5 Ncm (SD 10.2; 9-58) and its specifications according to jaws, bone quality and drilling protocol are reported in Table 2.

There was a moderate correlation between the last drill used at the implant surgery installation and the bone quality of the implant site ($R = -0.638$, $R^2 = 0.407$, $P < 0.001$; Spearman correlation). Suture were removed after 2 weeks, No implants presented signs of inflammation.

3.3 | Marginal bone loss (MBL)

The difference of MBL between the IL and AL groups was statistically significant at 6M and 1Y in relation to baseline, as reported in Table 3. There was no difference in MBL, between smokers and non-smokers or between implants of different diameters.

3.4 | Clinical findings

3.4.1 | Plaque index (PI)

PI scored 1 in 0.4% of 476 of sites at BL (2 sites); 9.9% at 6M (47 sites); 13.9% at 1Y (66 sites). No PI scored 2 or 3 were registered.

3.4.2 | Bleeding on probing (BoP)

BoP was present at BL in 242(50.8%) out of 476 sites. At 6M and 1Y BoP was registered in 271(56.9%) and in 227(47.7%) out of 476 sites respectively. The difference between the two groups was statistically significant (Table 4). The presence of BoP increased with time in IL group while it decreased in AL group. The main changes happened between BL and 6M in the IL sites, and between 6M and 1Y in the AL sites.

Of the 476 sites, 66 presented plaque and 227 presented BoP, and 54 presented at the same time plaque and BoP at 1Y. This means that 81.8% (54/66) of the sites with plaque had BoP, but only 23.8% of the sites with BoP presented plaque. The correlation between BoP and plaque was weak ($R = 0.274$, $R^2 = 0.075$, $P < 0.001$; Spearman correlation).

TABLE 3 Comparison of marginal bone loss (MBL) between the groups implant level and abutment level at different time

Group	MBL (mm) ^a Mean $\pm$ SD (min, max)		
	IP-BL	BL-6M	BL-1Y
IL	-0.148 $\pm$ 0.312 (-1.66, 0.00) (n = 57)	-0.106 $\pm$ 0.334 (-0.78, 1.42) (n = 51)	-0.086 $\pm$ 0.313 (-0.81, 1.17) (n = 58)
AL	-0.103 $\pm$ 0.234 (-0.90, 0.01), (n = 60)	-0.018 $\pm$ 0.214 (-0.95, 0.58), (n = 59)	-0.005 $\pm$ 0.222 (-0.99, 0.58), (n = 61)
P-value ^b	0.178	0.002	0.003

Abbreviations: AL, abutment level; BL, final prostheses delivery; IL, Implant level; IP, Implant placement; MBL, marginal bone loss.

^a Negative values indicate vertical bone loss, and positive values indicate vertical bone gain.

^b Mann-Whitney test.

TABLE 4 Comparison of bleed on probing of different implant faces between the implant level and abutment level groups at different time points

	BoP Yes/total (%)		P-value ^a
	IL	AL	
BL			
Mesial	25/58 (43.1)	41/61 (67.2)	0.008
Buccal	25/58 (43.1)	39/61 (63.9)	0.023
Distal	28/58 (48.3)	30/61 (49.2)	0.921
Lingual	25/58 (43.1)	29/61 (47.5)	0.686
Total	103/232 (44.4)	139/244 (57.0)	0.006
6M			
Mesial	36/58 (62.1)	41/61 (67.2)	0.557
Buccal	36/58 (62.1)	34/61 (55.7)	0.483
Distal	31/58 (53.4)	34/61 (55.7)	0.802
Lingual	29/58 (50.0)	30/61 (49.2)	0.929
Total	132/232 (56.9)	139/244 (57.0)	0.988
1Y			
Mesial	33/58 (56.9)	23/61 (37.7)	0.036
Buccal	41/58 (70.7)	22/61 (36.1)	<0.001
Distal	31/58 (53.4)	26/61 (42.6)	0.237
Lingual	28/58 (48.3)	23/61 (37.7)	0.244
Total	133/232 (57.3)	94/244 (38.5)	<0.001
	P-value ^a	P-value ^a	
BL - 6M ^b	<0.007	1.000	
6M - 1Y ^c	0.925	<0.001	
BL - 1Y ^d	<0.005	<0.001	

Abbreviations: AL, abutment level; BoP, bleed on probing; BL, Final prostheses delivery; IL, Implant level; IP, Implant placement.

^a Pearson's chi-squared test.

^b Comparison of the incidence of BoP sites of between BL and 6M for the respective groups.

^c Comparison of the incidence of BoP sites of between 6M and 1Y, for the respective groups.

^d Comparison of the incidence of BoP sites of between BL and 1Y, for the respective groups.

3.4.3 | Probing pocket depth (PPD)

The mean PPD at BL, 6M and 1Y and the difference between the two groups are reported in Table 5. There was a statistically significant difference of PPD between IL and AL group for all the sites at all follow-up time points. Moreover, the PPD significantly decreased with time in the AL group but not in the IL group.

3.4.4 | Keratinized mucosa (KM)

In general, there was a tendency towards decrease of buccal keratinized mucosa with time. Only the molar sites presented a statistically significant difference in width of the buccal keratinized mucosa between the two groups. The correlation between the width of keratinized mucosa and MBL at 1Y was very weak ($R = -0.038$, $R^2 = 0.001$, $P = 0.700$; Pearson correlation). Data are presented in Table 6.

3.5 | Complications

One abutment loosening occurred at BL. The abutment was secured using a torque wrench, before the final FPD delivery. One chip-off

fracture was reported in the IL group (position 23) and it was resolved by polishing. Thus, the overall failure rate of the screw retained FPD at 1Y was 2%.

4 | DISCUSSION

In this preliminary 1-year report of a randomized clinical trial, the authors investigated possible differences in hard and soft tissue response between IL and AL screw-retained FPD supported by implants with conical connection.

A greater amount of MBL is reported to occur in the early stage of healing. During the first year, perimplant bone remodeling could be influenced by several factors such as surgical procedures, numbers of surgical stages, repetitive disconnections during prosthetic procedures, type of implant connection and the establishment of the supra-crestal tissue.³³⁻³⁵

According to present findings, it was observed better results in marginal bone maintenance and soft-tissue parameters around AL

TABLE 5 Comparison of probing pocket depth of different implant faces between implant level and abutment level groups at different time points

	PPD mean $\pm$ SD (min-max)		P-value ^a
	IL	AL	
BL			
Mesial	3.76 $\pm$ 0.885 (2-6)	3.41 $\pm$ 1.230 (1-6)	0.043
Buccal	3.31 $\pm$ 0.568 (2-5)	2.87 $\pm$ 1.072 (1-6)	0.001
Distal	3.48 $\pm$ 0.903 (2-6)	2.89 $\pm$ 0.950 (1-6)	<0.001
Lingual	3.40 $\pm$ 0.857 (2-6)	2.72 $\pm$ 0.819 (2-6)	<0.001
Total	3.49 $\pm$ 0.827 (2-6) (n = 232)	2.97 $\pm$ 1.056 (1-6) (n = 244)	<0.001
6M			
Mesial	3.67 $\pm$ 0.747 (2-5)	3.27 $\pm$ 1.362 (1-8)	0.007
Buccal	3.40 $\pm$ 0.894 (2-5)	2.73 $\pm$ 1.080 (1-7)	<0.001
Distal	3.51 $\pm$ 0.879 (2-6)	2.98 $\pm$ 1.106 (1-6)	0.001
Lingual	2.91 $\pm$ 0.674 (2-4)	2.53 $\pm$ 1.023 (0-6)	0.001
Total	3.37 $\pm$ 0.848 (2-6) (n = 220)	2.88 $\pm$ 1.177 (0-8) (n = 236)	<0.001
1Y			
Mesial	3.81 $\pm$ 1.011 (2-6)	2.64 $\pm$ 1.119 (1-6)	<0.001
Buccal	3.37 $\pm$ 1.186 (1-7)	2.45 $\pm$ 0.829 (1-6)	<0.001
Distal	3.50 $\pm$ 1.005 (2-6)	2.77 $\pm$ 1.191 (1-6)	<0.001
Lingual	3.15 $\pm$ 0.979 (1-6)	2.52 $\pm$ 1.191 (1-7)	<0.001
Total	3.46 $\pm$ 1.069 (1-7) (n = 216)	2.59 $\pm$ 1.092 (1-7) (n = 224)	<0.001
	P-value ^a	P-value ^a	
BL - 6M ^b	0.230	0.217	
6M - 1Y ^c	0.571	<0.001	
BL - 1Y ^d	0.594	<0.001	

Abbreviations: AL, abutment level; BL, Final prostheses delivery; IL, implant level; IP, implant placement; Max, maximum; Min, minimum; PPD, probing pocket depth.

^a Mann-Whitney test.

^b Comparison of PPD between BL and 6 mo, for the respective groups.

^c Comparison of PPD between 6 mo and 1 y, for the respective groups.

^d Comparison of PPD between BL and 1 y, for the respective groups.

TABLE 6 Comparison of the width of the buccal keratinized mucosa (mm) the groups implant level and abutment level at different time points

	KM		P-value ^a
	IL	AL	
BL			
Incisive	-	2.00 ± 0.00 (2-2) (n = 5)	-
Canine	2.00 ± 0.00 (2-2) (n = 3)	2.00 ± 0.00 (2-2) (n = 2)	1.000
Premolar	1.96 ± 0.209 (1-2) (n = 23)	1.87 ± 0.344 (1-2) (n = 23)	0.301
Molar	1.81 ± 0.397 (1-2) (n = 32)	1.71 ± 0.461 (1-2) (n = 31)	0.342
6M			
Incisive	-	2.00 ± 0.00 (2-2) (n = 5)	-
Canine	2.00 ± 0.00 (2-2) (n = 2)	2.00 ± 0.00 (2-2) (n = 2)	1.000
Premolar	1.95 ± 0.213 (1-2) (n = 22)	1.62 ± 0.740 (0-2) (n = 21)	0.063
Molar	1.94 ± 0.250 (1-2) (n = 31)	1.48 ± 0.677 (0-2) (n = 31)	0.001
1Y			
Incisive	-	2.00 ± 0.00 (2-2) (n = 4)	-
Canine	2.00 ± 0.00 (2-2) (n = 2)	2.00 ± 0.00 (2-2) (n = 2)	1.000
Premolar	1.85 ± 0.366 (1-2) (n = 20)	1.45 ± 0.759 (0-2) (n = 20)	0.059
Molar	1.86 ± 0.351 (1-2) (n = 29)	1.43 ± 0.626 (0-2) (n = 30)	0.003

Abbreviations: AL, abutment level; BL, final prostheses delivery; IL, implant level; IP, implant placement; KM, keratinized mucosa buccal site; Max, Maximum; Min, Minimum.

implants both at 6 and 12 months after loading, thus null hypothesis was rejected. These results highlight how periimplant tissue response could be influenced by the FPD design after 1 year of function.

Even though the magnitude of MBL between the groups may be of limited clinical relevance, a statistically significant difference was observed between the implants in the IL group in comparison to the AL group. This trend is corroborated by a 5-year prospective study which investigated the role of the interposition of the abutment in the fixation implant-supported FPD,³⁶ in which statistically higher bone resorption during the first year of follow-up was reported around abutment-free implants. This initial alteration of the marginal bone level, though, was not followed by further modification after 3 and 5 years, regardless of the fixation mode.

Concerning the soft tissue, the IL group presented a significant worsening in BoP and PPD with time, while there was a significant improvement in the AL group. After 6 months and 1 year, the difference between the groups resulted to be statistically significant.

This finding is in line with a 5-years clinical trial investigating the use of an intermediary abutment for a full-arch rehabilitation. After 5 years of loading BoP was statistically higher in the abutment free group.³⁷

In clinical terms, these results suggest that periimplant soft tissue shows less inflammation and higher stability in AL group in the early follow-up phase. Interestingly, it was found that a greater number of sites were positive to BoP in AL compared to IL at BL. However, the design of the present study could not explain such finding.

The difference in hard and soft tissue between the groups can be justified by a number of possible explanations.

Firstly, the IL group was subjected to a prosthetic procedure that included the repeated unscrewing and screwing of the components. In an *in vivo* study, Abrahamsson³⁸ reported that recurrent abutment change interferes with the biological width, damaging the peri-implant

connective tissue. It was hypothesized that this repetitive soft tissue disruption would expose the peri-implant compartment to bacterial contamination, resulting in a worsening of the inflammatory status and eventually in a more pronounced marginal bone resorption,³⁹ according to the host response.⁴⁰ Differently, in the AL group, the definitive abutment was placed at the second surgery and then never removed. This procedure may allow the soft tissue to create a mucosal barrier and protect the osseointegration. The maturation of the soft tissue is a gradual process. Histological studies *in vivo*⁴¹ and on human tissue⁴² reported that the connective fibers became organized in 4-6 weeks, while the epithelium layer is completed in 6-8 weeks. This means that the prosthetic procedures in the IL group might have interfered with the maturation process.

Secondly, the better tissue conditions observed in the AL group can be explained by the response to the material of the components. Peri-implant tissues in the AL group were in direct contact to the titanium abutment, while in the IL group, tissues faced the Co/Cr framework structure. Even if the Co/Cr is considered biocompatible, an *in vitro* study reported that the viability of the epithelium cells as well as fibroblast was superior when in contact to titanium than to Co/Cr.⁴³ However, there is still no strong evidence on the clinical response of hard and soft tissues to Co/Cr frameworks.⁴⁴

A third explanation of the results could be related to the implant-abutment connection. IL screw retained restorations were produced with a modified implant-abutment interface design. To allow a frictionless seating of the framework into its final contact with the implant, index-free interfaces were manufactured. Moreover, according to the existing inter implant inclination, an additional reduction of the height interface contact was requested. Thus, a shortened contact between the framework and implant walls can prevent the benefits provided by a conical connection since, this modification is often arbitrary and it may not be validated from the implant manufacturer.¹³

Potential mechanical impairments and/or leakage phenomena may have caused the peri-implant soft tissue inflammation in the IL group.¹⁶ On the other hand, the AL group can take the full advantage of the complete implant-abutment engagement.⁴⁵ The scarce correlation between the PI and BoP would confirm that the peri-implant inflammation was associated to the type of prosthetic connection. However, it must be said that according to previous reports, soft tissue parameters, such as BoP and PPD, may not reflect the actual peri-implant health condition.⁴⁶

A limitation of the present study was that the inter-implant angulation was not considered. It is acknowledged that IL screw-retained reconstruction requires a great effort in order to have a passive fit, especially when implants are not placed parallel.^{5,47} As reported previously,⁴⁸ misfit generates areas of high peak stresses in the implant walls. This condition could cause mechanical complications, such as screw loosening or implant fracture.

A long-term follow-up period is needed to investigate the potential soft and hard tissue reaction at the two set-ups tested in this clinical trial.

5 | CONCLUSION

Within the limitations of this study we can conclude that a low grade of MBL was present in implant supported FPD after 1 year. Implant level connection showed significantly greater amount of MBL and soft tissue inflammation indexes compared with abutment level connected FDP. The results of this 1-year RCT suggest that, FPD at abutment level may be a safer procedure than at implant level setup in order to preserve a peri-implant tissue health. Long-term results are needed to confirm the present results.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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III

Title: Fixed full-arch maxillary prostheses supported by four versus six implants with a titanium CAD/CAM milled framework: 3-year multicentre RCT

Running Head: Four versus six implants in the maxilla rehabilitation.

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Author contributions:

MT: conceptualization, treated patients, collected data, analysed the data, wrote the original manuscript. MS: analysed the data and reviewed the manuscript. EC: treated patients, collected data, analysed the data. JPB: analysed the data and reviewed the manuscript. AW: analysed the data and reviewed the manuscript. DC: conceptualization, treated patients, collected data, analysed the data, and reviewed the manuscript.

Abstract

Objectives: This RCT compares marginal bone level (MBL) change and the clinical parameters after a 3-year function in maxillary implant-supported fixed complete dentures (FCDs) treated with four-implants(4-I) or 6-implants(6-I).

Material and method: Three centres treated 56 patients with 280 implants allocated to the 4-I or 6-I group. Radiographic and clinical examinations were performed. The primary outcome was to investigate MBL change between the groups.

Results: Implant survival rates were 100% and 99% in the 4-I and 6-I groups, respectively. Considering the clustering effects, the MBL change was not significantly different between the groups over the 3-year follow-up. The MBL in the 4-I group was $0.30\pm0.50\text{mm}$ at baseline, $0.24\pm0.31\text{mm}$ at 1-year and $0.24\pm0.38\text{mm}$ at 3-year. In the 6-I group, MBL was $0.14\pm0.32\text{mm}$ at baseline, $0.16\pm0.35\text{mm}$ at 1-year and $0.12\pm0.26\text{mm}$ at 3-year. There was a statistically significance difference between the groups at BL and 3Y. No significant differences between the groups were reported for clinical parameters at each time point as well as in between the visits. The technical and biological complications rates were 1.6% and 6.0%, respectively. Prosthetic complications affected 25 FCDs (47.2%).

Conclusion: MBL change revealed a stable condition in the 3-year period in the two groups. Few technical and biological complications occurred apart from chipping/fracture of the prosthetic teeth. Four-implant is a feasible solution if the rehabilitation is oriented towards the most cost-effective treatment and towards avoiding bone augmentation procedures. Clinicians have to consider the potential required visits for prosthetic maintenance.

Word count: 245

Keywords: marginal bone loss; four implants; edentulous maxilla edentulous; complications.

Introduction

Treatment of maxillary edentulism with implant-supported fixed complete denture (FCD) is a well-established and well-documented procedure(Adell, et al. 1990, Adell, et al. 1981, Branemark, et al. 1995, Jemt & Johansson 2006, Mertens, et al. 2012), offering superior comfort, masticatory function, and patient satisfaction compared to a complete denture(Oh, et al. 2016, Zitzmann & Marinello 2000). A recurring challenge for the maxillary FCD, is a reduced bone volume available for the implant placement(Cawood & Howell 1988, Lundqvist & Carlsson 1983). One approach is to augment the alveolar process bone volume, allowing the placement of an optimal number of implants in an ideal position(Adell, et al. 1990, Breine & Branemark 1980, Lambert, et al. 2009). However, bone augmentation techniques can be surgically invasive and associated with complications, such as donor site morbidity and risk of infection, and they involve longer increase of treatment times and higher costs(Becktor, et al. 2004, Chiapasco, et al. 2006, Esposito, et al. 2006). Irrespective of whether bone augmentation is performed or not, there is still a lack of evidence in the literature regarding the optimal number of implants required to support an FCD in the edentulous maxilla(Heydecke, et al. 2012, Lambert, et al. 2009).

Treatment protocols involving the use of fewer implants have been proposed as an alternative to bone augmentation and have shown acceptable clinical results(Adell, et al. 1981, Agliardi, et al. 2008, Aparicio, et al. 2006, Aparicio, et al. 2001, Del Fabbro, et al. 2012, Malo, et al. 2005). The promising clinical outcome of protocols in which four implants are used to support an FCD seems to indicate that placement of more implants may not be necessary(Branemark, et al. 1995, Maló, et al. 2012, Maló &

Lopes 2011). Despite their relatively high survival rate, FCD are subject to frequent biological and technical complications, such as veneer fractures, abutment and screw loosening, loss of retention, and soft tissue complications(Att, et al. 2009, Papaspyridakos, et al. 2012, Pjetursson, et al. 2012). Currently, the literature is not entirely clear on whether or not the number of implants might be a parameter that affects the incidence of technical and biological complications, thus increasing the overall cost of prosthetic rehabilitation in the long-term perspective(Carlsson & Carlsson 1994, Gothberg, et al. 2003, Johansson & Palmqvist 1990, Walton & MacEntee 1997). The aim of this prospective randomised study was, therefore, to compare clinical outcomes of a maxillary FCD supported by four(4-I) or six(6-I) implants.

The primary objective of this 3-year report of a 5-year RCT was to evaluate and compare the radiographic marginal bone level (MBL) change between the 4-I and 6-I group after three years of function. Furthermore, as a secondary objective, the difference in clinical results between the groups was evaluated in terms of soft tissue status, rate of technical/mechanical and biological complications and implant survival. The null hypothesis was that the 4-I group would perform as well as the 6-I group in rehabilitating patients with edentulous maxilla in terms of the MBL change of the implants.

Material and methods

Study Design

This multicentre RCT complied with the Helsinki Declaration(Association 2001). The CONSORT 2010 statement was followed as a guideline when reporting the outcomes(Schulz, et al. 2010). The study protocol was approved by the Medical Ethics Committee “Azienda U.L.S.S. N.16”, Padova, Italy (N.14161), and was registered at

the US National Institutes of Health (Clinicaltrials.gov): NCT02405169. The study was conducted in three private clinics located in Northern Italy. At each centre, an expert clinician performed the surgical and prosthetic procedures and collected the data.

Patient characteristics

Patients with maxillary edentulism as well as with an anatomical bone morphology suitable to accepting six implants, were selected. For the pre-screening evaluation, the patients' data, medical histories, and clinical and radiographic examination results were recorded. For treatment planning purposes, computed tomography (CBCT) scans, plaster cast models, and diagnostic wax-ups were acquired. If the patient's denture was unsuitable for realignment, a new denture was manufactured. Patients were included in this trial based on the following criteria: age ≥ 18 years; healthy patients (ASA-1) or mild systemic disease (ASA-2)(Wolters, et al. 1996); willingness to comply with all study requirements and to sign informed consent; and acceptable oral hygiene defined as full mouth scores $\leq 25\%$ (O'Leary, et al. 1972). The following criteria were used for exclusion: bone defects associated with severe knife-edge ridges; severe malocclusion, i.e., skeletal class III or class II deep-bites patients that required orthognathic surgery; bone defects resulting from tumour resection; smoking more than ten cigarettes per day; history of radiotherapy in the head and neck region; undergoing chemotherapy for treatment of malignant tumours at the time of the surgical procedure; uncontrolled diabetes; mucosal disease in the areas to be treated; and non-compliant patients.

Fifty-six patients met the above-reported criteria and were included in the study.

Patients (30 females, 9 smokers) with a mean age at the day of the surgery of 67 years (range 48-89 years) were treated with 280 implants between April 2013 and September

2015. Twenty-eight patients (17 males, 3 smokers), with a mean age of 64.6 years (range 51-81) were included in the 4-I group, while 28 patients (19 females, 6 smokers) with a mean age of 69.6 years (range 48-89) were included in the 6-I group.

As opposite dentition, 22 patients (39%), 11 in each group, presented FCD; 15 patients (six in the 4-I group and nine in the 6-I group) had natural dentition; 14 patients (eight in the 4-I group and six in the 6-I group) had fixed partial prostheses on implants in the posterior regions and natural dentition in the frontal area; four patients (two in each group) had natural dentition in the frontal area and removable denture in the posterior segments of the mandible; one patient in the 4-I group had an overdenture on two implants.

The patients were informed and asked to give their written informed consent before enrolment in the study. All patients received careful oral hygiene instructions and training in self-performed plaque control. The patients were randomly allocated to the 4-I or 6-I group, as shown in the study flow diagram (Figure 1). The randomisation was performed according to a manually generated restricted list, and sealed opaque envelopes were used to assign each patient to their allocated group on the day of the implant installation.

Surgical procedures

One hour prior to surgery, all patients received antibiotic prophylaxis (Amoxicillin, 2 gr). Antibiotic therapy was continued after surgery, 2 gr twice a day for 6 days. In the case of hypersensitivity to penicillin, different antibiotics were prescribed.

At surgery, the patients were required to rinse with chlorhexidine 0.2% for 1 minute. After infiltration with local anaesthesia, a crestal incision was performed, and a full-thickness buccal and palatal flap was elevated. Implant sites were prepared and implants (Astra Tech Implant System OsseoSpeed TX Dentsply Sirona Implants,

Mölndal, Sweden) were placed according to the manufacturer's instructions. One hundred and twelve implants were placed in the 4-I group received implants and 168 in the 6-I group. The implants diameter and length specifications are reported in Supplementary Tables 1 and 2, respectively. In cases where the most distal implant needed to be tilted, the implants were angulated parallel to the anterior wall of the sinus (Kallus, et al. 1990). The cover screws were placed, and the flap was carefully closed and sutured to obtain full periosteal coverage. The implants were installed with a two-stage surgical procedure with a conventional healing period. The patients were instructed to rinse with chlorhexidine 0.2% daily for 2 weeks and were advised to take NSAIDs for pain relief if needed and not to wear removable dentures for 2 weeks after surgery. Two weeks after surgery, the dentures were relined (Visco-gel, Dentsply-Sirona, Milford, USA) and the patients could wear them until the second stage surgery. During the first 8 weeks, patients were advised to follow a soft diet.

Prosthetic procedures

After 8 weeks (± 2) of healing, the implants were uncovered and the patient's prostheses were realigned. One implant in the 6-I group failed, and the treatment for the patient continued on five implants. Transmucosal external connection abutments with different heights (45° UniAbutment, Dentsply Sirona Implants, Mölndal, Sweden) were seated and secured at 20 Ncm. The abutment height was selected clinically depending on the thickness of the mucosa and/or the available inter-occlusal space and was divided into five lengths (Supplementary Table 3). Trans-mucosal healing caps (ProHeal Cap, Dentsply Sirona Implants, Mölndal, Sweden) were seated onto the abutments. After another 2 weeks (± 1) of soft tissue healing, the transmucosal external connection abutments were tightened at 20 Ncm and an impression was taken using screw-retained pick-up transfers (45° UniAbutment Pick-up, Dentsply Sirona

Implants, Mölndal, Sweden), with a customised impression tray and a polyether material (Impregum™ 3M Oral Care, St. Paul, MN, USA).

The technician made a verification index connecting the pick-up transfers with gypsum on the master cast that was screwed in the patient's mouth to verify the position of the implants in the master model(Toia, et al. 2019). Thereafter, the final set-up, based on to teeth position, occlusal registration, and vertical dimension, was sent to the milling centre (Atlantis Superstructures, Dentsply Sirona Implants, Hasselt, Belgium) for the manufacturing of a milled Titanium framework. After a review process of the framework design, the milled frameworks were sent back to each lab and were veneered with commercially available denture resin (Premium, Heraeus Kulzer, Hanau, Germany) or composite custom teeth (DEI® lab MCM, DEI Italia S.r.l., Mercurio, Italy)(Toia, et al. 2019). Each prosthesis contained teeth from the first right molar to the first left molar, giving a teeth-implant ratio of three in the 4-I group and 2 in the 6-I group supporting 12 teeth. If required, distal cantilevers were included in the prosthetic design, with their presence and length depending on the span between the implants, amount of vertical and transversal space, the position of the holes, and opposing arch dentition. The screw-retained prostheses were designed to access for hygienic maintenance. Eight ($\pm$ 2) weeks after abutment connection, the definitive screw-retained maxillary FCD was delivered, and each abutment and bridge screw were secured using a torque wrench at 20 Ncm. All the prosthetic procedures were performed in accordance with the manufacturer's instructions and product manuals (Figure 2-3).

Radiographic examinations

Periapical radiographs were taken at baseline (BL), on the day of the delivery of the definitive FCD, and after 1Y and 3Y, with FCD in situ. The radiographs were taken

with a digital X-ray apparatus supplied with a long cone. Rinn positioning systems were used to ensure the reproducibility of the measurement of the marginal bone height(Strid 1985). The radiographs were analysed and the MBL was measured by an independent and experienced radiologist at the Department of Radiology (Sahlgrenska Academy, Gothenburg University, Sweden) according to the procedure described by the same authors in a previous publication(Toia, et al. 2019). The MBL change was defined as the difference between the measured MBL at BL, 1Y, and 3Y. The radiographic length of the distal cantilever was calculated. The angle (tilting) of the distal implants with respect to the occlusal plane was calculated on the radiographs, and implants with an angle $\geq 15^\circ$ were considered “tilted”(Apaza Alccayhuaman, et al. 2018).

Clinical examinations

The implant sites were clinically examined using a calibrated periodontal probe (PCP 15; Hu-Friedy Manufacturing Co, Chicago, IL, USA) and the presence of plaque, bleeding, pockets(Parpaola, et al. 2015), and keratinised mucosa (KM) was recorded. In particular, the plaque index (PI) and bleeding on probing (BoP)(Mombelli, et al. 1987, Salvi & Lang 2004), were registered at each implant site on four surfaces (buccal, palatal, mesial, distal). The KM was registered as “0” (“absent” no KM meaning that the gingival margin consisted of lining mucosa), “1” (“partial” presence of KM <2 mm) and “2” (“complete” presence KM >2 mm)(Wennström, et al. 1994). In addition, the prosthetic integrity, the presence of plaque on the prostheses, and the status of the mucosa under the prostheses were recorded.

Follow-up protocol

The BL for clinical and radiological examinations was set on the day of the delivery of the definitive FCD. The same clinical and radiographical examinations were

performed at the 1-year (1Y) and 3-year (3Y) follow-up timepoints. The clinical parameters were collected before the final delivery at BL and after removal of the prostheses, which were unscrewed at each visit. Therefore, the implant stability at each visit was used to define the survival rate. The maxillary FCD survival rate was defined as the percentage of FCD placed at the BL and present at each visit.

During the duration of the study the patients visited a dental hygienist every six months for maintenance therapy, consisting of professional cleaning, oral hygiene instruction, and motivation (Corbella, et al. 2011).

Complications

The complications that occurred during the study were recorded for each implant and patient as follows:

- Technical/Mechanical complications affecting the prostheses: chipping and/or fracture of the veneering material; the presence of plaque on the prostheses; abutment-framework connection gaps; mobile prostheses; and framework fracture.
- Technical/Mechanical complications affecting the implants: mobility or fracture of the bridge screw and/or of the abutment screw; and an implant fracture.
- Biological complications affecting the prostheses comprised soft tissue inflammation in the edentulous area.
- Biological complications: mucositis (defined as BoP = 2) without any other signs, fistula, oedema, hyperplasia, and periimplantitis (Berglundh, et al. 2018).

Data analysis

This RCT was performed following a non-inferiority study design. It was assumed that a maxillary FCD on 4-I was not inferior to a maxillary FCD on 6-I. The MBL change was chosen as the primary endpoint for the analysis of statistical power. According to studies with similar patient selections, where six or more implants were used to support

a maxillary FCD, the mean bone loss after 1 year of function varied between 0.22 and 0.60 mm (Astrand, et al. 1999, Collaert & De Bruyn 2008). Therefore, use of the 4-I was considered non-inferior to 6-I for supporting a maxillary FCD, if the mean difference in MBL change between the groups after 1 year was not higher than 0.4 mm (SD 0.80) ($H_0: \mu < 0.4\text{mm}$; $H_1: \mu \geq 0.4\text{mm}$).

The sample size needed to give a power of 80%, an effect size d of 0.5, and an α -error of ≤ 0.05 (two-sided), was calculated as 24 patients in each group. Five patients per group were further included to account for possible withdrawals from the study, resulting in a target study population of 58 patients.

The patient characteristics, and status of the opposite dentition were recorded per patient. The MBL change, soft tissue indexes, implant survival, and prosthetic complication rates were reported for each implant.

Continuous variables were presented by mean, standard deviation, median, minimum, and maximum values. Categorical and discrete variables were presented by frequency and percentage. The normal distribution was tested with the Shapiro-Wilk test. A modified intention-to-treat (MITT), meaning all participants included at base-line, 1-year visits and no data imputation for drop-out at the 3-year follow-up) (Donati, et al. 2018). Given that implants were clustered into subjects, data cannot be assumed as independent. Accordingly, a generalised linear mixed model was applied to evaluate differences between groups for the dependent variables (MBL change, PI, Bop, PPD). In detail, the group variable (4 vs 6) was included as the fixed effect and patients were included as the random effect. A further linear mixed model was conducted including the loss of KM between BL-1Y and BL-3Y as a categorical predictor (absent, partial or complete) on the influence of MBL change, PI, Bop, and PPD over time.

The statistical analyses were performed using the software package SPSS (IBM Corporation, Armonk, USA). Binary variables were evaluated using Fisher's exact test.

RESULTS

Three drop-outs, all in the 6-I group, were registered before the completion of the 3-year follow-up (Figure 1) and therefore, their implants were not included in the statistical calculations for the analysis at 3Y.

Demographics

Only one implant was lost at the second stage surgery in the 6-I group giving a survival rate of 99.4% at 3Y and 100% in the 4-I group. The difference was not statistically significant. The lost implant was not replaced, and the case was finalised with five implants. Of the total 112 posteriorly placed implants in both groups, 64 exhibited a tilted position (57.1%). The 4-I group reported 45 (80.4%) out of 56 posterior implants were tilted with a mean angulation of 26.27° (SD 7.97; min 15°-max 45°) while in the 6-I group, 19 (33.9%) out of 56 posterior implants were tilted with a mean angulation of 22.11° (SD 5.11; min 15°-max 30°).

The cantilever had a mean length of 11.79 mm (SD 4.60; min 2.18 mm - max 21.43 mm) in the 4-I group and a mean length of 8.47 mm (SD 4.57; min 0.00 mm - max 18.48 mm) in the 6-I group (Supplementary Table 4).

Radiographic parameters

Notably, beyond the clustering effects, there were no significant differences between the two groups in MBL change between BL-1Y, between BL-3Y and between 1Y-3Y (Table 1).

The MBL in the 4-I group was 0.30±0.50 mm at BL, 0.24±0.31 mm at 1Y and 0.24±0.38 mm 3Y. In the 6-I group, MBL was 0.14±0.32 mm at BL, 0.16±0.35 mm at 1Y and 0.12±0.26 mm at 3Y. There was a statistically significance difference between

the groups at BL and 3Y. The numbers and percentage of implants according to the marginal bone level (MBL) at each visit for all the implants put together and divided into each group is reported in Table 2.

The mean MBL change of straight and tilted implants was evaluated for all patients, and the difference was compared in order to assess if tilted implants had lost more bone. However, no statistically significant difference was observed in the MBL change of straight and tilted implants. The mean MBL change was evaluated based on the height of the abutments used, and no statistically significant difference was present among the groups.

Clinical findings

The clustering effects of patients resulted significant for all the soft tissue indexes.

Taking this into account, the analysis reported no significant differences between the groups for PI, BoP, and PPD at each time point or in between the visits (Table 3-4-5).

The presence of KM during each visit is reported in Table 6. It was also investigated whether sites with loss of KM between BL-1Y and BL-3Y had an influence on the MBL change, PI, BoP and PPD. Results showed that sites with a diminishing with of KM presented no significant differences in MBL change ($F(2, 253.750)=0.002, =.998$) in BoP ($F(2, 253.682)=0.156, p=.856$) and in the PI change ($F(2, 246.077)=2.709, p=.069$). The effect of a reduced KM value demonstrated a significant influence on the PPD ($F(2, 256.864)=4.743, p=.009$).

Technical complications affecting the prostheses

Chipping and/or Fracture of the veneering material

The complications are summarised in Tables 7 and 8 and are here reported in detail:

At 1Y, 12 patients (21.4%) reported complications with the prostheses. Six patients (4-I group) presented with the fracture of an entire prosthetic tooth. Four patients (6-I

group) presented with fracture of two prosthetic teeth each. Two patients (one in the 4-I group and one in the 6-I group) presented with chipping of a prosthetic tooth.

At 2Y, two further patients (3.6%) (one for each group) were found to have complications with the prostheses. The patient in the 4-I group, who also had a complication at 1Y, presented with two chippings, one in the same tooth as at 1Y. The patient in the 6-I group presented with a fracture of one prosthetic tooth.

At 3Y, an additional 11 patients had complications (for one patient, it was the second experience of a complication). Seven (six in the 4-I group and one in the 6-I group) had one tooth involved either as chipping (one patient) or as dentition fracture (six patients). One patient in the 4-I group had two teeth with chipping. One patient in the 6-I group had two tooth fractures. Two patients (one in each group) had three teeth fractures.

Prosthetic complications affected a total of 23 patients over the 3 years of the study; however, two patients experienced complications twice during the 3-year period, thus 25 patients experienced such problems, with a total complication rate of 47.2%. In 20 patients (35.7%), the prostheses had to be removed and sent to the lab for adjustment. The prosthetic complications occurred in 16 patients in the 4-I group (28.6% of the patients) and nine in the 6-I group (16%).

These groups of patients presented the following dentition in the mandible: 11 mandible FCDPs, 4 fixed partial prostheses on implants in the posterior regions and natural dentition in the frontal area, 3 natural dentitions in the frontal area and removable dentures in the posterior regions, 1 with natural dentition and 1 implant at position 36, 1 natural dentition in the frontal and molar and molar regions and implants in the premolars region and 3 natural dentitions (ND).

Because of the above-mentioned prosthetic complications, acrylic night-time resin occlusal splints (Dawson 2006) (Palapress® transparent, Heraeus Kulzer, Hanau, Germany) were given to seven patients.

Presence of plaque on the prostheses

Twenty-seven patients (16 in the 4-I group and 11 in the 6-I group) reported plaque on the prostheses at 1Y and 33 patients did so (21 in the 4-I group and 12 in the 6-I group) at 3Y.

Technical complications affecting the implants

At 1Y, one patient in the 4-I group presented with a loose bridge screw in one implant. At 2Y, one patient in the 4-I group presented with an abutment screw fracture in one implant. At 3Y, one patient presented with one bridge screw fracture in one implant, and one patient presented with the mobility of one bridge screw. Both patients were in the 4-I group. Thus, the overall rates of technical/mechanical complications at 3Y were 1.53% at implant level and 7.55% at the patient level.

Biological complications affecting the prostheses

Soft tissue inflammation in the edentulous area

At 1Y, nine patients (seven in the 4-I group and two in the 6-I group) presented with inflammation in the edentulous area, probably due to compression of the prostheses, and as a consequence, eight prostheses were realigned.

At 3Y, ten patients (seven in the 4-I group and three in the 6-I group) presented inflammation in the edentulous area, and six of them had already at 1Y. All the prostheses of these patients were realigned.

Biological complications affecting the implants

At 1Y, three patients reported complications. One patient in the 6-I group showed edema around two implants but no bone loss was reported at the BL, 1Y, and at 3Y.

One patient in the 4-I group presented with a fistula (no suppuration). The MBL of this implant was 0.28 mm at BL, 0.82 mm at 1Y, and 0.79 mm at 3Y. One patient presented with mucositis (BoP 2) around two implants. At 2Y, one patient in the 4-I group presented with periimplantitis at one implant. The implant showed pus, a BoP 3, edema, and hyperplasia. The MBL of this implant was 0.88 mm at BL, 0.93 mm at 1Y, and 2.60 mm at 3Y. The patient was treated, and the infection resolved (Figure 4).

At 3Y, nine patients reported complications. One patient had an edema around two implants at the 3Y recall (the same patient, and 2 implants, as reported at 1 Y in the 6-I group). One patient in the 4-I group had an edema in one implant. One patient in the 4-I group had a fistula in one implant. The same patient reported periimplantitis at 2Y (Figure 2D). The fistula remained probably as a consequence of the healing process. This patient also reported chipping of the prostheses in the same position at 3Y and was included in the prosthetic complications. Five patients presented with mucositis (Bop 2) around one implant. In total, at 3Y, 15 (5.74%) implants in ten (18.86%) patients were affected by biological complications. The biological complications were treated by cleaning of the implant sulcus and irrigation with sterile saline.

Discussion

The aim of this study was to investigate whether or not maxillary FCD supported by four implants is comparable to those supported by six implants in terms of MBL change, survival rate, and clinical parameters. The present findings revealed that both treatment approaches are successful regarding the maxillary rehabilitation after three years of service. The values of the MBL change observed in the current study were below the threshold needed to identify a relevant clinical difference between the groups and thus the null hypothesis was not rejected.

The MBL change, in the current study, was stable during the observation period. This trend is in accordance with those in recent studies on implants with a moderately rough surface supporting maxillary FCDs. Three previous studies with 3-year follow-up used the same implant system as in the present study. In a prospective study by Engquist et al.(Engquist, et al. 2002), an MBL change of -0.22 mm (± 0.14) at 1 year was reported, while no additional change was observed at 3 years. In another study on 25 patients by Collaert and De Bruyn(Collaert & De Bruyn 2008), a bone losses of 0.58 mm (± 0.58), 0.60 mm (± 0.53) and 0.72 mm (± 0.63) were reported at 6 months, 1 year and 3 years from the baseline respectively. Similarly, in a prospective study involving 51 patients, Thor and co-authors (Thor, et al. 2014) reported a bone losses of 0.45 mm (± 0.73) mm 0.44 mm (± 0.79) and 0.57 mm (± 1.12) at after 6 months, 1 year and 3 years from the baseline respectively.

The same trend for MBL change was observed when a different implant system was studied, such as Straumann® Tissue Level implants (Straumann Holding AG, Basel, Switzerland). In a 2-year clinical trial, 25 edentulous maxillae were rehabilitated with 146 implants, and it was reported a mean bone loss of 0.24 mm and 0.15 mm at 1 and 2 years were reported, respectively (Bergkvist, et al. 2004). With the same implant system, 24 patients edentulous in the maxilla were restored with 142 implants to support FCDs. The MBL was at 2.13mm at the BL, 2.54 mm at 1Y and 2.68 mm at 3Y (Fischer & Stenberg 2006).

To the best of the authors' knowledge, only one RCT on maxillary FCD has previously compared the use of four and six implants. In this study, 40 patients were enrolled and 200 NobelSpeedy Groovy implants (NobelBiocare AG, Balsberg, Switzerland) were used(Tallarico, et al. 2016). Similar to our findings, a very limited difference in MBL

change between the groups was reported: 0.08 mm (± 0.05), 0.00 mm (± 0.07), and 0.03 mm (± 0.03) between 0-12 months, 12-24 months, and 24-36 months, respectively.

In the evaluation of the MBL change, the influence of some clinical factors was considered, such as the presence of a cantilever, implant inclination, and the use of a transmucosal abutment. In our study, the distal cantilever had a mean length of 10.1 mm and it was longer in the 4-I group than in the 6-I group (Supplementary Table 4). The MBL change of the distal implant-supporting cantilevers, however, did not differ from those of the other implants. This data corroborates previous studies where it was reported that the effect of the cantilever did not affect the MBL change (Storelli, et al. 2018, Wennstrom, et al. 2004).

Furthermore, the inclination of the posterior implants did not influence the MBL change, as similar results were obtained for tilted and axial implants over time, regardless of the group. This finding was confirmed by several studies that reported that inclining the posterior implants does not worsen their clinical outcome, in terms of implant survival rate and bone loss (Apaza Alccayhuaman, et al. 2018, Chrcanovic, et al. 2015, Del Fabbro, et al. 2012). Therefore, in the present study, the implant inclination was compensated for by the use of a transmucosal abutment.

It should be noted that the same type of intermediary one-piece abutment (Uni-abutment) was placed in all implants. According to a recent study (Toia, et al. 2019) the use of an intermediary abutment may preserve marginal bone levels. Moreover, the abutment design presented a straight profile, which allows for sufficient space to establish a proper vertical supra-crestal vertical dimension (Lazzara & Porter 2006). Furthermore, the abutment was seated at the second surgery and never removed, thus limiting the number of disconnection and re-connection procedures (Abrahamsson, et al. 2003). It was reported that this procedure might limit MBL loss (Borges, et al.

2018). Clinicians were also free to choose the height of the abutment that was most appropriate for the prosthetic restoration and mucosal vertical thickness, and MBL change presented similar values irrespective of the height of the abutments.

The implant survival rates in this RCT were very high in both groups (99.4% and 100% for the 6-I group and 4-I group, respectively) and were comparable with those of similar reports in the recent literature on maxillary implants (Drago 2018, Fischer & Stenberg 2006, Mertens, et al. 2012, Tallarico, et al. 2016).

However, when choosing a rehabilitation approach with a reduced number of implants, one concern is that losing a fixture may require an extra surgical procedure in order to substitute it. This is often considered unnecessary if the treatment strategy already involved six implants. In fact, the only patient that experienced implant loss in the present study (6-I group) could successfully be rehabilitated on the five remaining implants without additional surgeries. It must be said that the reported survival rate for maxillary rehabilitation sustained by four implants, according to the “all-on-4®” concept (Malo, et al. 2005) is very high, being 94.7% after 13 years of service (Maló, et al. 2019). The same author suggested that it is possible to achieve survival of the prostheses on three implants in the case of failure of one implant in a 4-I design (Maló, et al. 2012).

In terms of implant survival, there is no clear evidence on the optimal number for maxillary rehabilitation (Daudt Polido, et al. 2018). Because of the high anatomical heterogeneity of the edentulous maxillary arch, many options have been used and documented in the literature with implant numbers that ranges from 2 to 10 (Gallucci, et al. 2016). Arguably, the insertion of a higher number of implants than needed it might be considered as an over-treatment (Branemark, et al. 1995). On the other hand, successful edentulous maxillary rehabilitations have been reported with three or even

two implants (Cannizzaro, et al. 2017, Oliva, et al. 2012). However, the use of fewer than four implants remains controversial, as it often requires a prosthetic concept based on a shortened dental arch (Daudt Polido, et al. 2018).

One critical aspect to consider when proposing fixed bridges is the difficulty patients report in ensuring their hygienic maintenance (Pieri, et al. 2012). Despite the hygienic follow-up visits in this study, inadequate plaque control was observed in both groups in a relevant number of implant sites with an increase at longer follow-up (Table 3). Moreover, visible plaque was observed in the majority of the rehabilitations (27 prostheses at 1Y and 33 prostheses at 3Y) (Table 8). Notably, the presence of plaque in the 6-I group tended to be higher than in the 4-I group. This may indicate that the hygienic maintenance of a FCD supported by a greater number of implants is more complicated possibly owing to the reduced inter-implant space (Fortin, et al. 2002, Maló, et al. 2012).

Plaque control has been shown to be a primary factor in the long term-prevention of peri-implant disease (Serino & Strom 2009). Arguably, one could question whether implant-supported overdentures might have been a more suitable type of rehabilitation, especially in elderly patients with reduced dexterity and visibility (Yao, et al. 2018, Zitzmann & Marinello 2000). The cleaning and maintenance of both implants and prostheses may be easier with removable restorations than fixed ones (Martín-Ares, et al. 2016).

Nevertheless, the higher PI of the 6-I group did not result in a worse clinical outcome compared to the 4-I group, and indeed no statistical difference in BoP was observed between the two groups at 1Y and 3Y. In addition, a slightly lower PPD was observed for the 6-I implants compared to the 4-I implants at all timepoints. This difference, which was less than 0.3 mm, however, can be considered of minor clinical relevance

In our study, the KM exhibited a tendency to reduce over time. However, such a finding was not related to a worsening of the soft and hard tissue change. The role that KM plays when it comes to the health status of peri-implant tissues is debated. Although it has been reported that a lack of KM is associated with less favourable peri-implant conditions (Wennström, et al. 1994), in a recent retrospective study, it was reported that the width of the KM presented no correlation with the MBL, BoP, and PPD (Lim, et al. 2019), yet it was claimed that the presence of the KM facilitates personal care maintenance (Jepsen, et al. 2015). None of the other recorded clinical parameters were associated with an increase in MBL change. The role of the clinical parameters on bone loss prediction is controversial as revealed by previous studies. The clinician should be cognisant of possible false-positive findings (Coli, et al. 2017, Doornewaard, et al. 2018, Hashim, et al. 2018, Krebs, et al. 2019).

Complications

Few abutments and bridge screw loosening /fractures occurred and very few biological complications were reported with a rate of 1.53% and 5.74%, respectively with no difference between the groups (Table 6). The data corroborate the findings by Pjetursson and co-authors (Pjetursson, et al. 2012) where the abutment or screw loosening and the abutment or screw fracture presented a complication rates of 5.3% and 1.3% after 5-year respectively. The same authors reported a rate of 8.5% for biological complications.

However, prosthetic complications in the form of chipping or fracture of the veneering materials were a common finding, being observed in 12 patients (21.4%) in the first year and in 13 (24.5%) patients in the two following years (Table 10). The incidence

of prosthetic complications was similar between the two groups, with the number of implants having no impact on the incidence. Chipping and fracture of prosthetic teeth and veneering materials are reported to be very common among patients with FCDs (Jemt 1991, Jemt & Johansson 2006, Jemt & Lekholm 1995). In a meta-analysis on the complication rates on FCDs, it was reported that after 15 years of service, 70% of all the prostheses reported some form of veneering fracture (Bozini, et al. 2011). Similar findings with different variable rates were observed in different studies by several other authors: 45.8% (McGlumphy, et al. 2019), 39.7% (Heydecke, et al. 2012), 23.2% (Francetti, et al. 2015) and 10% (Tallarico, et al. 2016). Chipping rates seem to be higher for metal-resin restorations, such as in the current study, compared to metal-ceramic (Pjetursson, et al. 2012) or all ceramic, as confirmed by recent publications (Bagegni, et al. 2019, Barootchi, et al. 2020, Papaspyridakos, et al. 2019). One possible explanation for the high rates of fracture of the veneered teeth could be connected to laboratory techniques such as an improper thickness of the material or an under-dimensioned design of the milled framework, which reflects in unpaired stress between the resin matrix and the core of the suprastructure (Bozini, et al. 2011, Drago 2018, Drago & Howell 2012). However, the occurrence of complications was not correlated to the extension of the cantilever confirming what was reported in a four-year retrospective study on the use of cantilevers for full-arch titanium milled framework, in which prosthetic complications were a rare event (Drago 2018). Another possible explanation is that the vast majority of the fractures occurred in correspondence to the screw access hole where the framework is, in some cases, extremely under-dimensioned, representing the weakest point of veneering fracture (El-Haddad, et al. 2020, Gothberg, et al. 2003). A third possible reason for fractured veneered teeth is related to the jaw. The maxilla presents different biomechanisms with

more fractures of the veneered teeth than the mandible does (Bozini, et al. 2011, Carlsson & Carlsson 1994, Jemt 1991, Johansson & Palmqvist 1990). Moreover, 11 (47.9%) patients with chipping or prosthetic tooth fractures presented an FCD as an antagonist, indicating a possible lack of proprioception during jaw function. Finally, it has to be noted that a possibly incorrect jaw relation registration during the prosthetic steps may have increased the occurrence of complications (Cooper, et al. 2005, D. Mericske-Stern, et al. 2000).

In most cases, veneering material fractures are reversible complications that can be resolved with the restoration of the existing prostheses and stabilisation of the occlusion. None of the technical complications observed compromised the overall survival of the FCD, which was 100% in the current study corroborating data reported in literature (Maló, et al. 2012, Tallarico, et al. 2016). However, complications should be taken into consideration because they affect the overall costs of the treatment, jeopardizing short- and long-term success both for the dental clinic and for the patients and affecting patients' satisfaction with the treatment (Gallucci, et al. 2016, Walton & MacEntee 1997).

Based on the result of the present RCT, 4-I and 6-I perform equally well after 3 years of loading. In both groups, a limited MBL change and a high survival rate were observed, indicating the high predictability of such a type of treatment. Nevertheless, the patient performed hygienic maintenance, which might be easier in the 4-I group compared to the 6-I group. From a cost-effective point of view, this study may suggest that a 4-I solution may be more appropriate for the edentulous maxilla. The total cost of 4-I treatment implies a reduced financial exposure for patients or services (Babbush, et al. 2014). Moreover, a bone regeneration procedure might not be necessary, thus also reducing surgical invasiveness as well. For these reasons, a 4-I FCD may provide

major accessibility to fixed rehabilitation of the edentulous population (Maló, et al. 2012). Therefore, a clinician should be aware of the aforementioned aspects when choosing a treatment plan (Gallucci, et al. 2016). The high rate of prosthetic complications, though, should be carefully considered, as this will increase the total cost of the treatment.

Limitations

This RCT presents a number of limitations. Firstly, a 3-year follow up can be considered as a limited time in which to evaluate the success of prostheses and the biological complications (Berglundh, et al. 2018). However, it should be noted that our primary criterion of comparison between the two groups was the MBL, which is known to be more pronounced during the first years of function. The second limitation is the lack of X-ray analyses between implant placement and base-line. The vast majority of bone resorption is reported to occur during the first year of function, (Adell, et al. 1981, Astrand, et al. 2004) and such an evaluation might have explained the impact of the temporary complete denture on the MBL in the early stage of healing. The third limitation is the study population, which was selected by strict inclusion and exclusion criteria, and was followed up regularly with frequent recalls and maintenance. This population might not entirely reflect the real population of patients encountered by clinicians in their daily practice (Friberg & Jemt 2015). Future studies with long-term follow ups are required to confirm the present findings.

Conclusions

Within the limitations of the present study, it is suggested that fixed prosthetic rehabilitation of the fully edentulous maxilla by means of screw-retained CAD/CAM titanium frameworks can be successful whether they are supported by four or six implants. The MBL change revealed a stable bone level condition over the three years

of service. In addition, very few technical and biological complications occurred, whilst the occurrence of prosthetic complications (tooth chipping/fracture) was rather high. The findings of this RCT study suggest that, if the rehabilitation of the edentulous population is oriented to the most cost-effective treatment, the 4-I solution has to be considered as the most appropriate. However, clinicians have to be aware of not only of the initial cost of the therapy but also the potential for additional visits, and thus additional costs, required for the prosthetic maintenance.

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Table 1. Marginal bone level (MBL) (mm) mean±DS (95% Confidence interval)(Minimum-Maximum) for all the implants in the two groups at each visit and the MBL change (mm) mean±DS (95% Confidence interval)(Minimum-Maximum) between visits.

4-Implants					6-Implants				Group difference	
	<i>n</i>	Mean±SD	95% CI	min-max	<i>n</i>	Mean±SE	95% CI	min-max	<i>F</i> -value (a)	<i>P</i> -value (a)
BL	112	0.30±0.50	(0.21/0.40)	(0.00/2.34)	167	0.14±0.32	(0.09/0.18)	(0.00/1.949)	4.222	.045*
1Y	112	0.24±0.31	(0.18/0.29)	(0.00/1.14)	167	0.16±0.35	(0.11/0.22)	(0.00/2.20)	1.352	.250
3Y	112	0.24±0.38	(0.17/0.31)	(0.00/2.60)	149	0.12±0.26	(0.08/0.17)	(0.00/1.41)	4.933	.031*
BL-1Y	112	0.07±0.36	(0.00/0.14)	(-0.58/1.57)	167	-0.03±0.28	(-0.07/0.02)	(-2.20/1.14)	2.830	.099
BL-3Y	112	0.06±0.45	(-0.02/0.14)	(-1.72/1.46)	149	0.01±0.30	(-0.04/0.06)	(-1.41/1.94)	0.527	.472
1Y-3Y	112	-0.01±0.27	(-0.06/0.04)	(-1.67/0.76)	149	0.01±0.18	(-0.02/0.04)	(-0.88/0.80)	0.511	.478

Note. n: number of implants. Negative values represent Bone Loss. (a) Linear Mixed Model.

Table 2. Numbers and percentage divided in 6 groups according to the Marginal Bone Level (MBL) mm from the reference point in each visit for all the implants polled together and divided in each group.

	0 mm		0.01mm-0.5mm		0.51mm-1.00mm		1.01mm-1.50mm		1.51mm-2.00mm		>2.00mm		Total	
Total	N. Implants		N. Implants		N. Implants		N. Implants		N. Implants		N. Implants		N. Implants	
BL	191	68.5%	48	17.2%	24	8.6%	9	3.2%	5	1.8%	2	0.7%	279	100%
1Y	179	64.2%	57	20.4%	35	12.5%	5	1.8%	2	0.7%	1	0.4%	279	100%
3Y	173	66.3%	56	21.5%	26	10.0%	5	1.9%	0	0.0%	1	0.4%	261	100%
4-Implant Group														
BL	62	55.4%	28	25.0%	12	10.7%	5	4.5%	3	2.7%	2	1.8%	112	100%
1Y	61	54.5%	28	25.0%	21	18.8%	2	1.8%	0	0.0%	0	0.0%	112	100%
3Y	64	57.1%	27	24.1%	19	17.0%	1	0.9%	0	0.0%	1	0.9%	112	100%
6-Implant Group														
BL	129	77.2%	20	12.0%	12	7.2%	4	2.4%	2	1.2%	0	0.0%	167	100%
1Y	118	70.7%	29	17.4%	14	8.4%	3	1.8%	2	1.2%	1	0.6%	167	100%
3Y	109	73.2%	29	19.5%	7	4.7%	4	2.7%	0	0.0%	0	0.0%	149	100%

Table 3. Plaque Index (PI)(%) for all the implants in the two groups and the difference between them.

4-Implants				6-Implants			Group difference	
	<i>n</i>	Mean±SD	95% CI	<i>n</i>	Mean±SD	95% CI	<i>F-value (a)</i>	<i>P-value (a)</i>
BL	112	1.12±6.18	(-0.04/2.27)	167	3.74±18.74	(0.88/6.61)	0.509	.479
1Y	112	15.63±25.58	(10.83/20.42)	167	30.69±37.29	(24.99/36.39)	3.662	.061
3Y	112	20.54±27.92	(15.31/25.76)	149	31.54±35.76	(25.75/37.33)	2.245	.140
BL-1Y	112	-14.51±25.48	(-19.28/-9.74)	167	-26.95±35.35	(-32.35/-21.54)	2.722	.105
BL-3Y	112	-19.42±28.02	(-24.67/-14.17)	149	-31.38±35.97	(-37.20/-25.55)	2.635	.111
1Y-3Y	112	-4.91±32.33	(-10.96/1.14)	149	-2.35±34.18	(-7.88/3.18)	0.128	.722

Note. n: number of implants. (a) Linear Mixed Model.

Table 4. Bleeding on probing (BoP)(%) for all the implants in the two groups and the difference between them.

4-Implants				6-Implants				Group difference	
	<i>n</i>	Mean±SD	95% CI	<i>n</i>	Mean±SD	95% CI	<i>F-value (a)</i>	<i>P-value (a)</i>	
BL	112	41.07±40.67	(33.46/48.69)	167	29.64±36.47	(24.07/35.21)	1.755	.191	
1Y	112	51.12±36.20	(44.34/57.89)	167	48.65±37.05	(42.99/54.31)	0.128	.722	
3Y	112	45.98±33.48	(39.71/52.25)	149	46.81±38.37	(40.60/53.02)	0.013	.911	
BL-1Y	112	-10.05±45.58	(-18.58/-1.51)	167	-19.01±40.54	(-25.21/-12.82)	1.034	.314	
BL-3Y	112	-4.91±48.61	(-14.01/4.19)	149	-14.60±39.75	(-21.03/-8.16)	1.117	.296	
1Y-3Y	112	5.13±37.24	(-1.84/12.10)	149	-1.01±40.05	(-7.49/5.48)	0.722	.399	

Note. n: number of implants. (a) Linear Mixed Model.

Table 5. Probing pocket depth (PPD)(mm) for all the implants in the two groups at each visit and difference between visits.

4-Implants				6-Implants			Group difference	
	<i>n</i>	Mean±SD	95% CI	<i>n</i>	Mean±SD	95% CI	<i>F-value (a)</i>	<i>P-value (a)</i>
BL	112	3.28±0.89	(3.12/3.45)	167	2.91±1.12	(2.74/3.08)	3.472	.068
1Y	112	3.06±0.74	(2.92/3.20)	167	2.90±1.17	(2.72/3.08)	0.646	.425
3Y	112	3.07±0.78	(2.92/3.21)	149	2.80±1.07	(2.62/2.97)	1.855	.179
BL-1Y	112	0.22±0.67	(0.10/0.35)	167	0.01±0.51	(-0.07/0.09)	3.988	.051
BL-3Y	112	0.22±0.69	(0.09/0.35)	149	0.11±0.72	(-0.01/0.22)	0.651	.424
1Y-3Y	112	-0.01±0.58	(-0.11/0.10)	149	0.07±0.63	(-0.03/0.17)	0.383	.539

Note. n: number of implants. (a) Linear Mixed Model.

Table 6. Presence of Keratinised mucosa (KM) at different visits at the buccal side of each implant unit.

KM	Baseline				1Y				3Y			
	N	Absent %	Partial %	Complete %	N	Absent %	Partial %	Complete %	N	Absent %	Partial %	Complete %
Group												
4-I group	112	0	8.0	92.0	112	0	15.2	84.8	112	9.8	17.0	73.2
6-I group	167	0	19.8	80.2	167	0.6	22.8	76.6	149	12.8	20.8	66.4
Total	279	0	15.1	84.9	279	0.4	19.7	79.9	261	11.5	19.2	69.3

Table 7. Technical and Biological complications on the overall implants. (% N./Total Implants)

	1 Y	2Y	3Y	3 Year overall
Technical/Mechanical				% (N./Total Implants)
bridge screw loosening	1		1	0.77% (2/261)
abutment screw fracture		1	1	0.77% (1/261)
% (N./Total Implants)	0.36% (1/279)	0.36% (1/279)	0.77% (2/2261)	1.53% (4/261)
Biological				
Edema	2* (two implants in one patient)		1+2* (same patient at 1Y)	1.92% (5/261)
Fistula	1		1*(same patient at 2Y with periimplantitis)	0.77% (2/261)
Mucositis	2 (two implants in one patient)		5	2.68% (7/261)
Periimplantitis		1*		0.38% (1/261)
% (N./Total Implants)	1.79% (5/279)	0.36% (1/279)	3.45% (9/249)	5,74% (15/2261)

Table 8: Prostheses complications (% N./Total Prostheses)

	1 Y	2Y	3Y	3 Year overall
Prostheses				% (N/ Total Prostheses)
Chipping of the Veneering material	2§	1§(same patient at 1Y)	2	9.43% (5/53)
Fracture of the Veneering material	10¶	1	9¶ (same patient at 1Y)	37.74% (20/53)
% (N/ Total Prostheses)	21.43% (12/56)	3.57% (2/56)	20.75% (11/53)	47.17% (25/53)
Prostheses others				
Plaque on the prostheses	27/56		33/53	
Soft tissue inflammation in edentulous area	9/56		10/53	

Table 1 supplementary. Implants diameter (mm) specifications in each group.

Group	Implant Diameter				Total
	3.5	4	4.5	5	
4-I	20	82	6	4	112
6-I	60	67	31	10	168
Total	80	149	37	14	280

Table 2 supplementary. Implants length (mm) specifications in each group.

Group	Implant Length						Total
	6	8	9	11	13	15	
4-I	0	11	17	53	31	0	112
6-I	3	13	32	60	50	10	168
Total	3	24	49	113	81	10	280

Table 3 supplementary. Abutment length (mm) specifications in each group.

Group	Abutment Length					Total
	0.5	1	2	4	6	
4-I	12	28	60	8	4	112
6-I	4	23	118	17	5	167
Total	16	51	178	25	9	279
%/Total	5.7	18.3	63.8	9	3.2	100

Table 4 supplementary. Cantilever length (mm) in each group.

Group	Cantilever Length				
	N.	Mean	SD	Min	Max
4-I Left	28	12.02	4.34	2.23	20.10
4-I Right	28	11.56	5.69	0.00	24.29
4-I Total	28	11.79	4.60	2.18	21.43
6-I Left	28	8.59	4.91	0.00	18.48
6-I Right	28	8.36	4.93	0.00	17.24
6-I Total	28	8.47	4.57	0.00	18.48

Figure 1. Flowchart diagram of the study

Figure 2. Figures of a patient belong to the 4-implant group with x-rays at Baseline (BL), 1-year (1Y) and 3-year (3Y). A) Surgery. B) Healing of the soft tissue at baseline (BL). C) Titanium milled framework. D) Frontal view at BL. E) Frontal view at 3Y.

Figure 3. Figures of a patient belong to the 6-Implant group with x-rays at Baseline (BL), 1-year (1Y) and 3-year (3Y). A) Surgery. B) Healing of the soft tissue at baseline (BL). C) Titanium milled framework. D) Frontal view at BL. E) Frontal view at 3Y.

Figure 4: It reported a patient of the four-implant group. A) orthopantomogram at baseline. B) Clinical image of the patient. C) The patient at the 2-year visit presented periimplantitis at implant in position 21. D) The patient at the 3-year visit presented a fistula at the implant in position 21 (black arrow). E-F-G-H X-ray at visit Base-line, 1-year, 2-year, and 3-year respectively.

IV

Patient satisfaction and clinical outcomes in implant-supported overdentures retained by milled bars: Two-year follow-up

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Summary

Objectives: This observational clinical study evaluated the patient satisfaction and the clinical outcomes of edentulous arches rehabilitated with overdentures retained by CAD-CAM milled titanium bars.

Materials and Methods: Edentulous patients were treated with a full-arch removable overdenture anchored on two milled bars based on a friction retention system. Patient satisfaction was tested using the validated Oral Health Impact Profile (OHIP-14) questionnaire at the pre- and post-treatment visits, up to two years after prosthesis delivery (possible score range: 0-56. Best: 0). The prosthodontist satisfaction was also assessed through a designed questionnaire (best possible range 0-4. Best: 0). Radiographic and clinical examinations were performed at baseline and after 2 years of function. Implant and prostheses complications were recorded.

Results: Forty (25 mandible) edentulous patients, mean age 69 ± 9.5 (SD) (52% males, 10% smokers), were treated with a total of 185 implants. The mean difference between pre- and post-treatment OHIP-14 score was 20.6 ± 8.0 ($P < 0.0001$) showing a high level of satisfaction for aesthetics, functional and psychological outcomes. This perception was not influenced by patient's age or gender. The clinicians' mean score was 3.4 ± 4.0 . There was a marginal bone level (MBL) gain of 0.02 ± 0.22 mm between the two time points. Minor complications were reported in five patients.

Conclusions: This procedure may lead to satisfaction regarding aesthetics and mastication function. One of the most relevant aspects is the versatility, which allows selection of the most suitable treatment option according to patient needs. The prosthodontist satisfaction questionnaire showed that this procedure met the clinical expectations.

KEYWORDS

CAD-CAM, edentulous arch, implant, OHIP-14, overdenture, quality of life

1 | INTRODUCTION

Several authors have recently investigated the effect of reconstructive dentistry on patient Oral Health-Related Quality of Life (QoL),

as well as on the satisfaction of rehabilitated patients by considering the improvement of aesthetics, speech and ability of chewing.¹ Most studies have reported that in the recent years, edentulous patients represented the population receiving the main benefit by

the treatment with dental implants.^{2,3} Current scientific evidence suggests that, among edentulous patients, the greatest improvements concern the overall satisfaction, aesthetics, comfort, speech and the functional outcomes (mainly chewing ability and efficiency and bite force).

It has been reported that tooth loss is significantly associated with increasing age and may have negative effects on oral health-related QoL (OHRQoL).⁴⁻⁶ Comparing the efficacy of the treatment of edentulous patients with mandibular implant-retained overdentures versus conventional dentures among a cohort of middle-aged people, Awad et al have showed a significant improvement both in the physical and functional aspects as well as in the QoL, early after having received dental implants.⁷ However, in the oral implant literature, there are heterogeneous data on QoL and satisfaction outcomes in general. Furthermore, regarding this topic, mostly case series with small sample sizes have been recorded.⁸

When analysing the available scientific literature, it can be observed that patient-centred outcomes were retrieved from a variety of questionnaires either validated or not, that were self-reported or not. In view of the key role assumed by patient-centred outcomes in modern medicine, this poor validation may have significantly contributed to further increasing the heterogeneity of outcomes.⁹⁻¹² Most of the current studies reported to Oral Health Impact Profile index (OHIP) as a valuable tool for capturing the respondent's perception of the impact of oral health on the QoL.¹³ The complete OHIP includes 49 questions based on the Locker's mode.¹⁴ OHIP-14 has been proposed as a shortened 14-item questionnaire, and it is currently considered a valid clinical tool to evaluate patients' perception before and after treatment.¹⁵

In the literature, there is a relative lack of data about patient-centred outcomes for subjects treated with overdentures supported by CAD-CAM milled titanium bars. The limited data available were reported to be useful to fully restore functional occlusion and provide acceptable aesthetics. Due to the wide variety in therapy and design options, in addition to clinical outcomes, it becomes relevant to evaluate the patient's and clinician's satisfaction.

The main aim of the present observational study was to evaluate patient-centred outcomes in subjects treated with full-arch implant-supported removable dentures and to evaluate factors potentially influencing the patients' perception about the treatment. The secondary aims were to assess the changes of radiographic and clinical parameters, as well as mechanical, technical and biological complications, and to evaluate clinicians' satisfaction.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective investigation was performed in five different private clinics, four of which were affiliated to FRANCI Institute (Padova, Italy) and one affiliated to Malmö University (Malmö,

Sweden). Experienced clinicians (one at each centre) with a similar level of expertise performed the interventions.

The study protocol was approved by the Medical Ethics Committee Azienda Ospedaliera di Circolo Italy (VA) (N.000205-35815).

All subjects included were treated following the principles and the guidelines of the Helsinki Declaration of 1964, as revised in the subsequent years.¹⁶

2.2 | Sample characteristics

To be included, all patients had to fulfil the following inclusion criteria:

- Older than 18 years;

- Willingness and ability to comply with all study requirements, to sign the written informed consent form and to fill in the final questionnaire;

- Absence of systemic medical conditions that could represent relative or absolute contraindications to intervention (patients had to be ASA-1 or ASA-2 following the classification by the American Society of Anaesthesiologists);

- Patients with a vertical distance between the two arches sufficient to support the milled framework according to the framework design specifications.

- Good oral hygiene involving the residual opposite dentition defined as full mouth plaque score $\leq 25\%$.¹⁷

The following exclusion criteria were applied:

- History of radiotherapy in the head and neck region and/or chemotherapy for treatment of malignant tumours in the 12 months prior to the time of the surgical procedure;

- Smoking more than 10 cigarettes per day;

- Uncontrolled diabetes;

- Mucosal disease (such as oral lichen planus and epidermolysis bullosa), in the areas to be treated;

- Non-compliant patients;

- Situations that the main investigator considered unsuitable for the surgical treatment.

A total of 40 totally edentulous patients (eight for each centre) eligible to be treated with implants in at least one jaw were enrolled and scheduled to receive a full-arch removable dental prosthesis.

All patients provided written informed consent, after having been informed of the potential benefits and risks of the proposed implant treatment, and having discussed alternative options with the treating clinician.

2.3 | Surgical procedures

All patients received AstraTech ImplantSystem Osseospeed TX (TX) and AstraTech® Implant System Osseospeed EV (EV) (Dentsply Sirona Implants, Mölndal, Sweden) with two-stage approach. Two months later, implants were uncovered and a screw retained index free abutment (Uni® Abutment Dentsply Sirona Implants, Mölndal, Sweden) was seated.

FIGURE 1 Clinical case: (A) Model mock-up scanned with a set-up of 14 teeth. (B) Suprastructure (hybrid counter-bar) with retention pins (T-shape). (C) Mesostructure milled in two pieces

2.4 | Prosthetic protocol

The same clinician performed the surgical as well the prosthetic rehabilitation procedures at each centre. The prosthetic rehabilitation was performed two weeks after abutment connection. Hence, for the impression, an adequate transfer was housed.

Six weeks after impression, the definitive implant-supported overdentures rigidly retained with milled bars were applied. The lengths of bridge cantilevers were carefully calculated to guarantee a sufficient number of teeth according to the framework design specifications and opposite arch.

2.5 | Framework design specifications

After performing the correct set-up, the model and mock-up are sent to the milling centre to be scanned. A software elaborates a virtual design of two CAD/CAM milled titanium bars for overdenture ("2-in-1" Atlantis® Suprastructure Dentsply Sirona Implants, Mölndal, Sweden) (Figure 1A). The mesostructured is a fixed screw-retained bar on abutment level set-up and, if the arch presents at least six implants, could be milled in two pieces (Figure 1C). The suprastructure is a hybrid counter-bar inserted in the removable denture rigidly anchored on the mesostructured (Figure 1B). The suprastructure is produced with two different shape of retention pins (I-shape, Figure 2E and T-shape Figure 1B) to be finalised with custom teeth or denture resin (Figure 2D).¹⁸⁻²⁰

The retention between the two bars is guaranteed by the frictional force obtained by an angle of 4° conical design of the mesostructure. Additional retention elements could be included in the two bars in order to obtain optimal stability, according to patient's characteristics and to be mouldable according to patient's requests (Figure 2B,C,E).¹⁸

The two titanium bars request at least a minimum vertical space of 5 mm and a minimum of transversal space of 4 mm. These values are dependent on several circumstances such as span between the implants, cantilever length, type and amount of attachments.

2.6 | Measurement of OHRQoL with OHIP-14 modified version

A standard version of the OHIP-14 questionnaire was used, whose details are presented in Table 1. The questionnaire was filled out by patients before treatment, and the quality of life assessment was

repeated at one and three months, and two years after the placement of the prosthetic restoration.

Fourteen OHRQoL items were rated on a 0-4 scale (Never = 0; Hardly Ever = 1; Occasionally = 2; Fairly Often = 3; Always = 4). OHIP-14 is divided into seven areas of investigation according to the type of question: Q1-Q2 (functional limitation); Q3-Q4 (physical pain); Q5-Q6 (psychological discomfort); Q7-Q8 (physical disability); Q9-Q10 (psychological disability); Q11-Q12 (social disability); Q13-Q14 (handicap).

In each patient, the OHRQoL was defined by estimating the OHIP-14 summary score, that is, the sum of the 14 sub-scores (possible score range for patient satisfaction: 0-56) (best score = 0, worst = 56). High OHIP-14 scores indicate poor OHRQoL, whereas low OHIP-14 scores indicate satisfactory OHRQoL.

2.7 | Clinician satisfaction evaluation

Before the final prostheses' delivery, clinicians completed a satisfaction questionnaire.

Five questions were reported and in particular: Q1 Were the milled bars delivered on time?; Q2 Were the milled bars easy to build up the final prosthesis?; Q3 Did the milled bars fit well with the implants? Q4 Were the milled bars easy to disassemble? Q5 Did the milled bars meet your expectations?

Five factors were rated on a 0-4 scale (Very satisfied = 0; Satisfied = 1; Neutral = 2; Dissatisfied = 3; Very dissatisfied = 4). The sum of the five sub-scores for the prosthodontist was then calculated, ranging from 0 to 20 (best score = 0, worst = 20). Low scores indicate high satisfaction, suggesting how well the implant features declared by the manufacturer meet the prosthodontist's expectations.

2.8 | Radiographic and clinical evaluation

Clinical and radiographic examinations of the reconstructions were performed at the delivery of the final reconstruction, baseline (BL) and after 2 years of function, at follow-up (FU). Radiographs were taken with parallel technique with a Rinn® Universal Collimator (Dentsply Sirona RINN® York, PA, USA) to control exposure geometry at each visit to ensure reproducibility. The digital radiographs were analysed with a software (ImageJ, National Institutes of Health, Bethesda, MD, USA) The distance from the mesial and distal interproximal bone level to the reference point (implant shoulder, bevel) was measured to the nearest 0.1 mm, and a mean of these two

FIGURE 2 Clinical case: (A) Edentulous mandible with 4 implants in position. (B) Mesostructure, milled in one piece, directly screwed on abutment level connection with retention elements (Gold colour). (C) Suprastructure inserted inside the denture with retention frictional elements. (D) Final removal prosthesis in situ with a set-up pf 12 teeth. (E) X-ray evaluation of the final prosthesis where both the primary and secondary structures are evident. The frictional elements are present in the posterior segments (red arrows). It is visible in the suprastructure the retention pins (I-shape)

measurements was calculated for each implant to measure marginal bone level (MBL) changes. If the implant reference point was below the margin of the crestal bone, that is, subcrestal, the value was considered as ± 0 . Radiographs were taken at BL and at FU to evaluate the difference of MBL changes at the two time points.

The length of cantilever of the mesostructure and suprastructure was measured on the x-ray as the horizontal distance from the axis of the implant till the distal portion.

All measurements were performed by an independent radiologist not involved in the study. Intra-examiner measure variability was determined by re-examining 10% of all measures randomly selected, and the measurement error was calculated.

Peri-implant tissues health status was evaluated at BL and FU. The following parameters were evaluated: (a) presence of plaque (Yes/No) on the surfaces of each individual abutment; (b) probing pocket depth (PPD), assessed by measuring and recording the distance in mm (approximated to the nearest 0.5 mm) from the peri-implant mucosal margin to the bottom of the mucosal pocket, using a periodontal probe; (c) bleeding on probing (BoP) was assessed by inserting a periodontal probe to the bottom of the mucosal pocket (Yes/No). The aforementioned parameters were assessed with a periodontal calibrated probe (PCP 15; Hu-Friedy Manufacturing Co, Chicago, IL, USA).

Four sites per abutment/implant (facial/buccal, mesial, distal and lingual/palatal) were evaluated.

2.9 | Survival and complications

Implant and prosthesis survival was defined as an implant or a prosthetic reconstruction still in function at the time of observation.²¹

Any complication or failure related to the implant-supported restorations was recorded. Technical complications included loss of retention, prosthesis fracture and/or chipping, and framework

fracture. Mechanical complications included abutment and screw loosening or fracture and implant fracture. Biological complications included peri-implant mucositis, defined as an inflammation of the soft tissues surrounding the implant, without signs of any loss of supporting bone, and peri-implantitis, defined as the presence of an inflammatory lesion in the peri-implant mucosa associated with bleeding on probing and suppuration, and radiographic bone loss around implants. Failures included loss of implant and or loss of the implant-supported restoration.

2.10 | Statistical analysis

The implant was used as statistical unit, and the analyses were performed using a dedicated software (IBM SPSS Statistics for Mac, v.22). Continuous variables are presented by means of number of observations, mean and standard deviation, minimum, median, maximum, lower and higher quartile. Discrete variables are presented by frequency and percentage. The normality of outcome variables distribution was tested. Wilcoxon rank-sum test was used to compare the parameters regarding MBL and clinical parameter between BL and FU. Difference between the groups was evaluated with one-way analysis of variance (ANOVA).

The hypothesis that the length of cantilever could influence the MBL change of the distal implants was evaluated by comparing the difference of MBL change of the mesial implants with the distal implants, using the Wilcoxon rank-sum test. The null hypothesis was "there is no difference in marginal bone level change around mesial and distal implants supporting the prosthetic reconstruction".

The OHIP scores before and after treatment were evaluated using a repeated measure analysis of variance (ANOVA).

Multiple regression models were used to evaluate whether patient baseline characteristics (age, gender, smoking, diabetes)

TABLE 1 OHIP-14 questionnaire

OHIP-14 questions	Never	Hardly ever	Occasionally	Fairly often	Always
A) Functional limitation					
1) Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures?					
2) Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?					
B) Physical pain					
3) Have you had painful aching in your mouth?					
4) Have you had discomfort/pain in eating any food because of problems with your teeth, mouth or dentures?					
C) Psychological discomfort					
5) Have you been self-conscious because of your teeth, mouth or dentures?					
6) Have you felt tense because of problems with your teeth, mouth or dentures?					
D) Physical disability					
7) Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures?					
8) Have you had to interrupt meals because of problems with your teeth, mouth or dentures?					
E) Psychological disability					
9) Have you found it difficult to relax because of problems with your teeth, mouth or dentures?					
10) Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?					
F) Social disability					
11) Have you been irritable with other people because of problems with your teeth, mouth or dentures?					
12) Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?					
D) Handicap					
13) Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?					
14) Have you been totally unable to function because of problems with your teeth, mouth or dentures?					

influenced the pre-/post-treatment OHIP scores. Statistical significance was set at a value of probability $P < 0.05$.

3 | RESULTS

3.1 | Demographic outcome

Forty patients (52% males, 10% smokers), mean age 69 ± 9.5 (SD) years, range 49–88 years, were treated with a total of 185 implants. Twenty-five (62.5%) patients were treated in the mandible. Each patient received an average of 4.65 ± 1.2 implants (range 4 to 8 implants), and 100 implants (54.3%) were placed in the mandible. One hundred and twenty implants (65%) were TX, and sixty-five (35%) were EV designs.

Implants TX diameter and length are here reported: 3.5 X 8mm (3); 3.5 X 9mm (9); 3.5 X 11mm (19); 4.0 X 6mm (6); 4.0 X 8mm (2); 4.0

X 11mm (45); 4.0 X 13mm (26); 4.5 X 11mm (2); 4.5 X 13mm (4); 5.0 X 9mm (1); 5.0 X 13mm (3).

Implants EV diameter and length are here reported: 3.0 × 8 mm (2); 3.6 × 6 mm (3); 3.6 × 8 mm (1); 3.6 × 9 mm (1); 3.6 × 11 mm (8); 3.6 × 13 mm (5); 4.2 × 9 mm (9); 4.2 × 11 mm (27); 4.2 × 13 mm (9).

All implants were osseointegrated (survival rate 100%) and were clinically stable after 2 years of function.

The opposite dentition for each patient was also recorded, and in particular, 7 (17.5%) patients presented an implant-supported overdenture; 7 (17.5%) patients presented a complete denture; 6 (15%) patients presented a fix full-arch screw-retained implant support denture; 2 (5%) patients presented a partial denture supported by teeth; 11 (27.5%) patients presented natural dentition plus fixed partial denture teeth supported; 3 (7.5%) patients presented natural dentition plus fixed partial denture implants supported; 4 (10%) patients presented complete natural dentition.

FIGURE 3 Box-and-whisker plots of OHRQoL factors for the questionnaire dispensed pre- (A) and post-treatment (B: 1 month; C: 3 months; D: 2 years). In the box-and-whisker plot, the central box represents the values from the lower to upper quartile (25th–75th percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding “outside” and “far out” values, which are displayed as separate points

The mean cantilever length of the mesostructured (Figure 1B) was as follows: on the left side 8.39 ± 2.97 mm (range 0.00 to 13.66 mm); on the right side mean 8.57 ± 3.11 mm (range 0.00 to 13.94 mm). The mean cantilever length of the suprastructure (Figure 1C) was as follows: on the left side 10.22 ± 6.07 mm (range 0.00 to 19.60 mm); on the right side 10.44 ± 6.35 mm (range 0.00 to 22.08 mm). In both the bars, there was no statistically significant difference of cantilever length between left and right side ($P > 0.05$).

The numbers of teeth (units) of the overdenture's prostheses were 11 units in four (10%) patients, 12 units in twenty-seven (67%) patients (Figure 2D) and 14 units in nine (23%) patients (Figure 1A). Two (4%) patients present a mesostructure with two bars (Figure 1C) while thirty-eight (96%) patients presented one milled bar (Figure 2B).

The retention pins were milled with an I-shaped (Figure 2E) in nine (23%) and with a T-shaped (Figure 1B) in thirty-one (77%) suprastructures, respectively.

3.2 | OHIP-14 outcome

The median satisfaction scores for the 14 OHRQoL items assessed pre-treatment, 1 month, 3 months and 2 years post-treatment are summarised in Figure 3A–D. For all questions, the scores decreased significantly after treatment as compared to pre-treatment scores ($P < 0.0001$).

The mean pre-treatment OHIP-14 score was 22.88 ± 9.4 (range 1 to 44). After 1 month of treatment, the mean score was 2.25 ± 3.3 (range 0 to 18); after 3 months, the mean was 2.35 ± 3.9 (range 0 to 21); and after 2 years, it was 2.40 ± 3.9 (range 0 to 22). Figure 4 illustrates the OHIP-14 score summary throughout the study. At each follow-up, the scores were significantly different from the pre-treatment one ($P < 0.0001$), while they were not significantly different among them ($P > 0.05$).

Multiple regression models were computed to evaluate whether patient characteristics such as age, smoking, gender had an effect on the OHIP-14 summary score pre- and post-treatment or their difference (namely, the perception of QoL improvement). The results of such analyses showed that none of the patient's characteristics had a significant influence on OHIP scores or their difference.

3.3 | Clinician satisfaction outcome

On an average, the prosthodontists were very satisfied about the delivery and the versatility of the two milled bars, reporting a mean score of 3.4 ± 4 .

3.4 | Intra-examiner variability

Seventy-four measurements were randomly repeated at 4 months after the first evaluation. Sixty-nine (93.24%) of measurement discrepancies were less than 0.2 mm; two (2.7%) were between 0.21 and 0.4 mm; two (2.7%) were between 0.41 and 0.6 mm; and only one measurement discrepancy was higher than 0.6 mm.

3.5 | Radiographic parameters

The mean MBL change between BL and FU reported a crestal bone gain of 0.02 ± 0.21 mm (median 0.21 mm; min. -0.49 mm; max. to 1.19 mm). No statistically significant difference ($P > 0.05$) was observed between BL and FU (Figure 5).

FIGURE 4 Pre-treatment and post-treatment OHIP-14 score summary after 1 month, 3 months and 2 years

It was reported a statistically significant difference in MBL changes between TX and EV implants both at BL and FU as well as between FU and BL (Table 2).

The hypothesis that the length of cantilever could influence the MBL of the most distal implants was rejected since the difference between the MBL change of the distal implants and the mesial implants was non-statistically significant.

3.6 | Peri-implant mucosa status

Plaque was present on the surfaces of 34 site out 740 (4.6%) at BL and 55 sites out of 740 (7.4%) at FU. No statistical significance difference was observed between the two time points.

The mean PPD at baseline for all implants averaging all sites was 2.46 ± 1.01 mm (range 0.00 to 6.00 mm). At 2-year follow-up mean PPD for all implants, averaging all sites, was 2.46 ± 0.94 (range 0.00 to 6.00 mm). No statistically significant difference was observed between the two time points.

BoP was present on the surfaces of 114 site out 740 (15.41%) at BL and 165 sites out of 740 (22.30%) at FU. Statistically significant difference ($P = 0.032$) was present between BL and FU.

3.7 | Complications

Mechanical complications were reported in three patients. In detail: in one patient, two prosthetic screws lost their tightness in the mesostructure; two patients from different centres reported a lost friction between the two bars.

One patient reported a technical complication consisting of a chipping of the resin central lower left incisor.

Biological complications affected only one implant in one patient that presented a peri-implant mucositis. All complications

were considered minor and successfully addressed by the treating clinicians.

4 | DISCUSSION

Several studies and systematic reviews have recently evaluated how the patients may objectively perceive the effects of reconstructive dentistry on significant improvement of the quality of life.^{2,3} The main benefits have been reported for fully edentulous patients, which represent the most investigated population.^{8,22} These patients report that they are able to eat tougher foods thanks to their increased bite force and ability to chew.^{23,24}

Indeed, after receiving the prosthetic restoration, the immediate improvement in masticatory performance suggests a corresponding improvement of patients' nutritional and physical state.² Nevertheless, one study found a relevant patient satisfaction about denture comfort but the changes in dietary intake, nutritional state, body mass index (BMI) and blood markers were quite uncertain, and this aspect deserves further investigations.⁷

With regard to the particular restoration that was tested in the study, our results may suggest that such milled CAD/CAM bars could improve functional performance and aesthetic aspect, resulting in improved satisfaction of the patients and with a very low complication rate too.

In order to evaluate patient-centred outcomes, the questionnaire had to consider some important issues such as tooth loss (including functional limitation, physical pain, psychological discomfort and

TABLE 2 Marginal bone level (MBL mm) at baseline (BL) and follow-up 2 y (FU) and between the 2 time points (BL-FU)

	Visit	BL	FU	BL-FU
Total	Min.	0.00	0.00	1.19
	Max.	-1.78	-1.46	-0.49
	Mean	-0.30	-0.27	0.02
	Median	-0.14	-0.15	0.00
	SD	0.40	0.35	0.22
Type of implant				
Osseospeed TX	Min.	0.00	0.00	1.19
	Max.	-1.78	-1.46	-0.49
	Mean	-0.37	-0.32	0.05
	Median	-0.21	-0.18	0.00
	SD	0.45	0.40	0.25
Osseospeed EV	Min.	0.00	0.00	0.25
	Max.	-0.80	-0.81	-0.49
	Mean	-0.14	-0.17	-0.03
	Median	0.00	-0.11	0.00
	SD	0.18	0.21	0.11
P-value		0.000	0.009	0.022

Negative values correspond to crestal bone loss from the reference point of the implant.

FIGURE 5 Marginal bone level change at baseline (A) and after 2 years (B)

physical/psychological/social disability and aesthetic features). In addition, it is known that patient satisfaction may be modulated by individual characteristics, and it is thus relevant to adjust the subjective perception for age, gender, habits (eg smoking status) and systemic health (ie diabetes) to provide independent and objective evidence and address the influence of confounding variables. The questionnaires used in the present study were validated in a number of studies both in its complete form (with 49 items)²⁵ and in its short one (14 items).^{9,26}

In the present study, functional limitation, pain, psychological discomfort and impaired quality of life were the leading reasons for requiring implant restoration. In addition, a significant improvement of the QoL has been reported by all patients, and it was often associated with the early improvement of dietary habits. All patients were generally satisfied.

These results are comparable to those obtained in other studies with similar design. Pozzi and coworkers in 2016 reported one-year results of a prospective single-cohort study, using an analogue OHIP questionnaire, in patients with edentulous jaws treated with a four-implant overdenture supported by a CAD-CAM titanium bars.²⁷ Similar to the present study, they found a significant improvement of quality of life in all patients. Kouppala and Raustia in 2015 found excellent OHIP-14 results after treatment with full-arch maxillary restorations.²⁸ Moreover, some authors found that mandibular overdentures anchored to four implants were related to better OHIP-14 outcomes than those anchored to two implants.²⁹ This finding could support the hypothesis that the more stable the prosthesis is, the lower is the impairment of patients' quality of life. The excellent results found in the present study could also be related to the good prosthesis stability as, on an average, each prosthesis was supported by four or more implants. Another study by Oh and colleagues confirmed that oral health-related quality of life improved similarly for implant-supported fixed prosthesis and for implant-anchored overdentures as compared to removable dentures.³⁰ The authors stressed the importance to focus on patient-centred outcomes when choosing a treatment option.

A limitation of this study may be the lack of data about bite force and blood markers estimated before and after treatment, which could have provided more robust evidence on changes in the nutritional state of patients. Although the sample size is relatively low in our study, it is comparable to other reports of the current available literature.²⁶ Another limitation is related to the absence of a control group, which could reduce the generalisability of the results.

In this study, also the clinician's satisfaction was assessed. The results were optimal especially for the versatility of the two milled bars employed in this study. The subjectivity related to the individual answers provided by patients and clinicians to the questionnaires could be considered as an intrinsic limitation. However, we may underline that, in spite of the possible differences among the subjects involved, regarding perception of the various choices of the questionnaire, the general trend, for both patients and clinicians, pointed unanimously towards a full satisfaction regarding the procedure.

The CAD-CAM solution used in this study was capable of guaranteeing high prosthetic performance as well as high soft tissue health as suggested by the low marginal bone level change between baseline and follow-up visit. Even it was reported a statistically significant difference in crestal bone loss between the two group of implants, these results are in line with other studies that used similar implant system where only minor bone loss was reported after a follow-up of at least one year.³¹⁻³³

Only minor complications were reported and, remarkably, only one patient reported a chipping with this prosthetic solution as reported in similar studies that used the same retention concept.^{18,19}

We may hypothesise that this excellent result can depend on three facts as follows: (a) the size and strength of the mesostructure and of the suprastructure allowed a good stability of the prosthetic reconstruction; (b) the absence of holes in the reconstruction, as opposed to a classic screw-retained full mouth reconstructions, may limit the incidence of chipping or fractures of the composite or resin teeth (in fact, in screw-retained frameworks, the higher incidence of fracture is usually observed at the hole site, which is a weak point of the structures);³⁴ (c) the limited follow-up duration, being only two years; it is possible that with a longer follow-up some more complications may occur.

Besides, the main disadvantage of this type of rehabilitation was represented by the need for having enough space in the lingual-buccal dimension as well as between the two jaws concerning the possibility to have the two milled bars plus the space for the prosthesis teeth. A careful pre-treatment design of the prosthetic structure and a set-up of the final prosthesis were mandatory to precisely evaluate the amount of volume needed for the entire reconstruction.

This CAD-CAM based system is a valid alternative tool for patients with extremely atrophic arches (Figure 2) where the implant position could not be prosthetically driven. Moreover, the possibility to have a double cantilevered bars (one in the mesostructured and the second in the suprastructure) allowed the clinician to design an implant-supported prosthesis without the classic tissue support of overdentures. The characteristic resilient anchoring solution of an overdenture may induce continue resorption in the residual skeletal bone with possible complications and patient's discomfort.³⁵⁻³⁷ Two patients reported paraesthesia before the treatment probably due to the resorbed mandible with superficialisation of the alveolar nerve (Figure 2). With this solution, it was feasible to position implants in the interforaminal region giving to the patients the possibility to have a complete 12-teeth arch overpassing the compression to the nerve.

5 | CONCLUSIONS

In conclusion, our study suggested that this procedure achieved excellent results in terms of clinical outcomes and patient satisfaction. One of the most relevant aspects of this procedure is the versatility, which allows selection of the most suitable treatment option according to patient needs. In addition, the prosthodontist's satisfaction

questionnaire showed that the procedure fully met the clinical expectations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests. This publication's content is solely the responsibility of the authors.

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