Periodontal Health in Children with Juvenile idiopathic arthritis

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Abstract

Aim To investigate gingival inflammation and prevalence of four specific periodontal associated pathogens in Juvenile idiopathic arthritis (JIA) in relation to orofacial pain, jaw function and systemic inflammatory activity in JIA. **Method** Forty-five children with JIA and 16 healthy children as controls, were enrolled. Subjects were examined and classified according to the diagnostic criteria for temporomandibular disorders (DC/TMD). Pain, pain-related disability and jaw function were also assessed. A clinical periodontal examination was performed. Subgingival plaque samples were collected and analyzed for semiquantitative levels of the following periodontal pathogens; Aggregatibacter actinomycetemcomintans, Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola. **Results** No significant difference between JIA and healthy individuals was observed regarding the clinical periodontal variables plaque, gingivitis, probing pocket depth or the investigated periodontal pathogens. P. gingivalis and T. forsythia were detected in both groups. In the group with JIA, no significant correlation was found between orofacial pain, jaw function, systemic inflammatory activity and periodontal disease, including levels of P. gingivalis and T. forsythia. **Conclusions** This study suggests that the periodontal disease-associated bacteria P. gingivalis and T. forsythia do not contribute to neither periodontal disease, systemic inflammatory activity nor orofacial pain and jaw dysfunction, including TMJ arthritis, in JIA patients in Sweden.

KEYWORDS Bacteria anaerobic, children, juvenile idiopathic arthritis, periodontal disease, temporomandibular joint disorders.

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease defined as arthritis of unknown origin with onset before the age of 16 years and with symptoms or signs of arthritis persisting for at least 6 weeks. This systemic disease primarily affects the musculoskeletal system, where autoimmune reactions targeting synovial tissues may result in arthritis [Prakken et al., 2011]. There is limited knowledge available regarding the possible relation between JIA and periodontal health. A systematic review reported prevalence of degenerative joint disease, as a sign of joint involvement, in the temporomandibular joint (TMJ) in JIA-patients to vary between 40% and 93% [Pantoja et al., 2019]. In addition, the salivary flow rate has been found to be lower in children with JIA compared to healthy controls [Kobus et al., 2017]. These factors may adversely affect the ability to maintain satisfactory oral hygiene. Indeed, reduced oral hygiene has been reported in JIA-children 6–12 years of age [Feres de Melo et al., 2014]. The systemic inflammation caused by JIA may affect the inflammatory response in the periodontal tissues. Periodontal diseases are bacterially-induced inflammatory diseases. Periodontitis early in life is rare, with a reported prevalence of 0.1% for aggressive periodontitis in the permanent dentition in the European population [Bouziane et al., 2020]. An equally low prevalence has been described in Swedish children and adolescents [Sjödin et al., 1993]. On the other hand, for the mildest form of periodontal disease, gingivitis, a prevalence as high as 70% has been reported in children in general [Oh et al., 2002]. Gingivitis is more prevalent in children with JIA than in healthy controls [Merle et al., 2020]. Accordingly, JIA patients seem to have higher degree of bleeding on probing (BOP), even when plaque is under control [Grevich et al., 2019]. Several systemic diseases and immunological disorders have been linked to periodontitis in children and adolescents [Marchetti et al., 2022]. Theoretically, periodontal inflammation (gingivitis) may, on the other hand, influence JIA disease development. This has not been proved yet in JIA but there are indications of a possible influence on the disease activity in rheumatoid arthritis (RA) by periodontal inflammation. Infections has been proposed as one of several potential environmental triggers for RA onset [Carty et al., 2004]. RA has been linked to periodontitis but the findings are inconsistent. The primary etiologic factor for periodontal disease is a subgingival dysbiotic bacterial community, initiating host-pathogen interactions. Destructive immune system responses lead to ulceration of the gingival epithelium and, eventually, exposing the bacteria and their products to the bloodstream, thereby initiating or maintaining systemic inflammation [Hirschfeld and Kawai, 2015]. Periodontitis as a multimicrobial inflammatory disease in which the various bacterial species within the dental biofilm are in a dysbiotic state and imbalance, favors the establishment of chronic inflammatory conditions. Ultimately, this results in destruction of tooth-supporting tissues [Fragkioudakis et al., 2021]. An increased overall risk of periodontitis has been associated with RA [Tang et al., 2017]. In individuals with a genetic risk of developing RA, inflammatory periodontal involvement seems to be able to modulate the severity

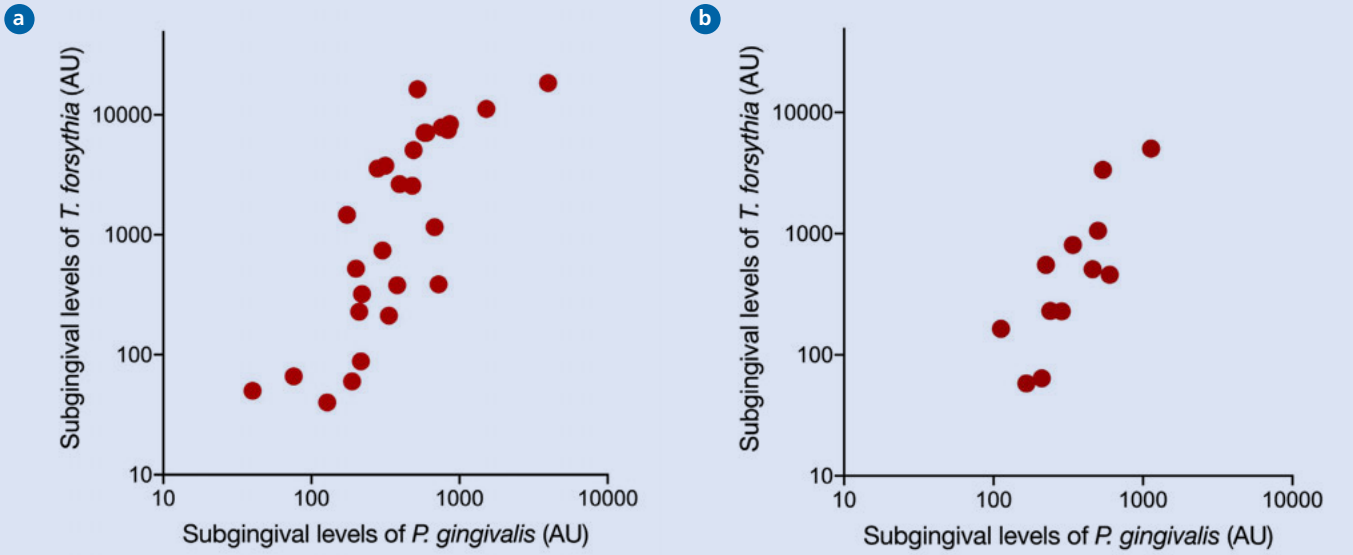

FIG. 1 A AND B Scatter-plot showing the relation between gingival crevicular fluid levels (AU) or *P. gingivalis* and *T. forsythia* in 45 patients with juvenile idiopathic arthritis (fig 1 a; rs = 0.66, n = 43, P < 0.001) as well as in 16 age- and sex-matched healthy individuals (fig 1 b; rs = 0.59, n = 16, P = 0.017).

of the clinical presentation of RA [Bello-Gualtero et al., 2016]. The general subgingival microbiota was described by Socransky in 1998, who observed that pocket depth was strongly related to prevalence of periodontitis-associated bacterial species in adults [Socransky et al., 1998]. *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), Porphyromonas gingivalis (P. gingivalis), Tannerella forsythia (T. forsythia) and Treponema denticola (T. denticola)* are species strongly associated with periodontal disease and can be considered as keystone pathogens [Ximénez-Fyvie et al., 2000]. Recent literature focus on the complexity of the microbial communities, including various bacterial species as well as other microbes such as oral fungi, maintaining the imbalance and the interaction between different species [Baker et al., 2017; Li et al., 2022]. In addition, immunological and genetic mechanisms, environmental factors and lifestyle factors further contributes to the complexity of periodontitis [Sedghi et al., 2021]. In the primary dentition, periodontal pathogens are infrequent but become established in conjunction with the permanent dentition [Cortelli et al., 2012]. In addition, *P. gingivalis* has been proposed to play a pathogenic role in RA, due to its ability to induce citrullination [Perricone et al., 2019]. Anti-citrullinated protein antibodies (ACPA) are strongly associated with RA and can be detectable years before onset of symptoms of RA [Johansson et al., 2016]. Indeed, *P. gingivalis* has been associated with presence of ACPA in JIA and ACPA-positive JIA patients have been shown to have higher antibody titers for *P. gingivalis* [Lange et al., 2016]. The aims of this study were to investigate gingival inflammation and the prevalence of four specific periodontal associated pathogens in JIA children and healthy peers and to study their relations to orofacial pain, jaw function and systemic inflammatory activity in JIA children.

Materials and Methods

Study Participants and Protocol

The study, conducted at the the Centre of Oral Rehabilitation Linköping, Sweden, between 2015 and 2018, had a case-controlled, cross-sectional study design. Forty-five JIA patients aged from six to 16 years (33 girls and 12 boys) were included (Table 1). The JIA patients were consecutively referred to our department from four pediatric departments in South-east Sweden (Linköping University Hospital, Linköping; Vrinnevi Hospital, Norrköping; Motala Hospital, Motala and Västervik Hospital, Västervik, Sweden). Inclusion criteria were JIA-diagnosis according to the criteria of the International League of Association for rheumatology (ILAR) [Petty et al., 2004]. Exclusion criteria were diabetes, inflammatory-bowel disease, other chronic pain condition than JIA and psychiatric disease (depression and anxiety were, however, allowed due to the frequent occurrence and significant role in chronic pain). Nineteen (43%) of the patients had oligoarthritis, 15 (33%) had polyarthritis and 11 (24%) had other subtypes of JIA (systemic arthritis, psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis). At time for inclusion, 34 patients were on anti-rheumatic therapy; 28 on methotrexate, 12 on biologics (adalimumab or etanercept) and seven on prednisolone. The patients without antirheumatic therapy were on NSAIDs or in remission. Disease activity was scored according to the 71-joint Juvenile Arthritis Disease Activity Score (JADAS71). A JADAS71 score higher than 4.0 is considered to represent high disease activity [Consolaro et al., 2016] (Table 1). Sixteen healthy age- and sex-matched individuals were recruited from the Public Dental Health clinic in Linköping, Sweden. Inclusion criteria were no subjective pain from the orofacial region. Exclusion criteria were rheumatic disease, diabetes, inflammatory-bowel disease, other chronic pain conditions and psychiatric disease (depression and anxiety were allowed). In compliance with the Helsinki Declaration, the Regional Ethics Committee at Linköping University, Linköping, Sweden (Dnr 2014/461–31) approved the study protocol. All patients and their parents provided written consent to participate in the study after ample oral information by the operator as well as written information and documentation.

Periodontal examination and subgingival microbial analyses

One of the authors (ADC) performed all examinations and data collections. Dental plaque-scores were calculated in percent based on the presence of visible plaque at the gingival margin on four surfaces (buccal, lingual, mesial, distal) of each tooth.

		PATIENTS				HEALTHY INDIVIDUALS			
		Percentiles				Percentiles			
		Media	25th	75th	n	Median	25th	75th	n
Individuals									
Age	years	12	10	15	45	13	10	13	16
Sex	boys/girl				12/33				5/11
Age at diagnosis	years	9	5	12	45	n.a.			
Disease duration	years	4	3	7	45	n.a.			
Disease activity									
JADAS71	0-101	6.0	2.8	9.8	45	n.a.			
Erythrocyte sedimentation rate*	mm/h	6	3	10	45	n.d.			16
C-Reactive protein*	mg/L	0	0	0	45	n.d.			16
Rheumatoid factor	U/mL	n.d.			45	n.d.			16
Antinuclear antibodies	U/mL	n.d.			45	n.d.			16
Anti-citrullinated antibodies	U/mL	n.d.			43	n.d.			16
DC/TMD diagnoses									
Myalgia	n				10				1
Myofascial pain with referral	n				2				0
Arthralgia	n (joints)				8				0
Headache attributed to TMD	n				3				0
Combinations from above									
Myalgia and arthralgia	n				2				0
Myalgia, arthralgia and headache	n				2				0

n = number of observations; n.a. = not applicable; n.d. = not detectable; JADAS71 = 71-joint Juvenile Arthritis Disease Activity Score; DC/TMD = diagnostic criteria for temporomandibular disorders.
**Values below detection limits for ESR (<30 mm/h) and CRP (<5 mg/L) were counted as 0.*

TABLE 1 Demographic data, disease activity and temporomandibular disorder diagnoses for 45 patients with juvenile idiopathic arthritis and 16 age- and sex-matched healthy individuals.

Periodontal pockets were recorded on six tooth-surfaces (mesio-buccal, buccal, disto-buccal, disto-lingual, lingual, mesio-lingual) if the pocket depth was ≥ 4 mm, using a manual periodontal probe (HuFriedyPCP11; manual periodontal probe PCP 11 (Hu-Friedy, Chicago, Illinois, United States). Since there were only a few pockets with a depth of ≥ 4 mm in our sample, the degree of inflammation was calculated in percent based on the pooling of sites with bleeding at the gingival margin or from the bleeding at the bottom of a deep pocket. Subgingival microbial plaque samples from the mesial surface of the first premolar, or a primary premolar, in each quadrant were collected as follows. Supragingival plaque was removed, the root surface was dried and a sterile endodontic paper-point was inserted into the pocket for 20 s.

From each subject, the samples were pooled into a sterile Eppendorf tube and transported to be assayed at the Department of Oral Microbiology and Immunology, University of Gothenburg, Sweden. A quantitative polymerase chain reaction assay (qPCR) [Morillo et al., 2004] was performed with the purpose to detect and quantify known sequences of DNA from the following periodontal pathogens; *A. actinomycetemcomintans, P. gingivalis, T. forsythia and T. denticola.*

Parotid saliva

Unstimulated parotid gland saliva was collected intraorally, using a modified Carlson-Crittenden collector [Dimitrijevic Carlsson et al., 2020]. The collector was placed directly over the papilla of Stensen's duct and parotid saliva was collected during passive drooling by the collector via a plastic tube into an Eppendorf Tube.

Collection time varied from five to 60 minutes, depending upon the time needed to collect a sufficient and adequate sample volume. Total sampling time and sample volume were recorded and salivary flow was calculated in mL/min.

Clinical examination of orofacial pain and temporomandibular disorders

The diagnostic classification of temporomandibular disorders (DC/TMD) was used to diagnose the patients and healthy individuals. The DC/TMD comprises two domains: Axis I for physical diagnoses and Axis II psychosocial distress, including several domains regarding pain and its consequences [Schiffman et al., 2014]. The clinical examination for Axis I diagnostics requires a pain and jaw noise history assessed using a questionnaire and a well-defined and structured clinical examination. The clinical examination evaluate familiar pain localizations, jaw movement capacity (lateral, protruding, and mouth opening), familiar jaw movement pain, TMJ noises and familiar pain upon palpation of the masticatory muscles and TMJ. DC/TMD can be used to classify the following most common TMD conditions: TMJ arthralgia, masticatory muscle myalgia, headache attributed to TMD, degenerative joint disease and TMJ disk displacements. Multiple diagnoses are allowed in DC/TMD. Orofacial pain intensity and pain-related disability were assessed by the characteristic pain intensity subscale and the pain-related disability subscale of the Graded Chronic Pain Scale questionnaire (composite measures of pain intensity for current pain, average pain and the worst pain during the last week as well as disability in general, at work and in social situations from the orofacial pain)[Von Korff et al., 1992]. Jaw function was assessed using the Jaw Functional Limitation Scale (JFLS-8). JFLS-8 contains eight items regarding the extent to which jaw pain or dysfunction limits normal jaw functions (jaw mobility, mastication as well as verbal and emotional expression) [Ohrbach et al., 2008].

Blood sampling

Venous blood samples were obtained to assess markers of

		PATIENTS					HEALTHY INDIVIDUALS				
		Percentiles					Percentiles				
		Median	25th	75th	%pos	n	Median	25th	75th	%pos	n
Periodontal status											
Plaque index	%	17	10	28	91	45	16	10	22	100	16
Gingival bleeding index	%	2	1	7	78	45	2	0	5	63	16
Parotid saliva flow	mL/min	0.016	0.007	0.020	n.a.	45	0.020	0.014	0.036	n.a.	16
Orofacial pain and jaw function											
Maximum mouth opening	mm	47	44	51	n.a.	45	51	48	53	n.a.	16
TMJ pain on maximum mouth opening	Y/N				15	6/39				0	0/16
Masticatory muscle pain on jaw movement	0-16	0	0	2	22	45	0	0	0	6	16
Number of sites with referred pain	0-12	0	0	0	7	45	0	0	0	0	16
Characteristic pain intensity	0-10	0	0	3	31	45	0	0	0	19	16
Jaw function limitation scale	0-80	0	0	3	33	45	0	0	0	19	16
Activity of daily living limitation	0.0-3.0	0.2	0.0	0.5	60	45	n.a.				
n.a.= not applicable; %pos = percentage of samples with data > 0 or > cut-off for normal of the total number of observations. Activity of daily life limitation was assessed with the Childhood Health Assessment Questionnaire.											

TABLE 2 Clinical (periodontal status, orofacial pain and jaw function) and psychosocial status from 45 patients with juvenile idiopathic arthritis and 16 age- and sex-matched healthy individuals

disease activity and relevant antibodies (erythrocyte sedimentation rate, C-reactive protein, rheumatic factor, anti-nuclear antibodies and anti-citrullinated antibodies). These samples were analysed at a routine and accredited medial laboratory at the Linköping University Hospital, Linköping, Sweden. The Juvenile Arthritis Disease Activity Score (JADAS71) was calculated by the paediatrician or paediatric rheumatologist and it is based on active joint count, physician's global assessment, parental global evaluation, and erythrocyte sedimentation rate [Consolaro et al., 2009].

Statistics

Non-parametric statistics were used due to the characteristics of many of the included variables. For descriptive statistics, the results were expressed as median as well as 25th and 75th percentiles. In order to calculate the significance of differences between groups, the Mann-Whitney U-test was used. The Spearman rank correlation was to calculate the significance of the correlations between signs and symptoms in the JIA patients versus periodontal variables or presence/absence of periodontal pathogens. A probability level ≤ 0.05 was considered statistically significant.

Results

Clinical variables

Table 2 report descriptive data of the clinical variables regarding periodontal status as well as orofacial pain and jaw function in the JIA patients and healthy individuals. The JIA patients had lower parotid saliva flow rate (P = 0.039; Table 2). There was no statistically significant difference between the patients and the healthy individuals regarding the other investigated variables.

Subgingival microbiota

Table 3 presents data on bacterial levels of *P. gingivalis, A. actinomycetemcomitans, T. denticola* and *T. forsythia*. There was no significant difference in presence or levels of the investigated bacteria between the JIA patients and the healthy individuals.

The parotid saliva flow was not significantly correlated to any of the investigated subgingival bacterial species.

Relations between presence of subgingival bacteria versus clinical variables

Subgingival levels of *P. gingivalis* and *T. forsythia* were significantly related (rs = 0.66, n = 43, P < 0.001; Fig. 1A) in the JIA patients as well as in the healthy individuals (rs = 0.59, n = 16, P = 0.017; Fig. 1B). In the JIA patients, plaque index was significantly related to subgingival levels of *P. gingivalis* (rs = 0.40, n = 45, P = 0.007), *T. denticola* (rs = -0.84, n = 10, P = 0.003) and *T. forsythia* (rs = 0.41, n = 43, P = 0.007). These relations were not found in the healthy individuals on a significant level. The plaque index and the gingival bleeding index were significantly related in the JIA patients (rs = 0.58, n = 45, P < 0.001) as well

		PATIENTS					HEALTHY INDIVIDUALS				
		Percentiles					Percentiles				
		Median	25th	75th	%pos	n	Median	25th	75th	%pos	n
Bacteria											
Aggregatibacter actinomycetemcomintans	AU	n.d.			0	16	n.d.			0	3
Porphyromonas gingivalis	AU	212	80	490	96	45	263	184	510	100	16
Tannerella forsythia	AU	228	0	3360	65	43	229	44	616	75	16
Treponema denticola	AU	0	0	92	40	10	n.d.			0	1
AU = arbritary unit; %pos = percentage of samples with detectable levels of respective bacteria in the total number of samples for each bacteria; n.d. = not detectable.											

TABLE 3 Bacterial levels in gingival exsudates from 45 patients with juvenile idiopathic arthritis and 16-age and sex-matched healthy individuals.

as in the healthy individuals (rs = 0.62, n = 16, P = 0.010). In the JIA patients, the subgingival level of *P. gingivalis* was significantly related to CRP (rs = -0.41, n = 45, P = 0.035). Neither *T. denticola, T. forsythia*, plaque index nor gingival bleeding index were significantly related to any of the clinical variables. In the healthy individuals, there were no significant correlation between the sublingual levels of the investigated bacteria versus the clinical variables.

Discussion

This study could not show that the investigated clinical periodontal variables differ between JIA children and healthy controls. Neither were there any significant no differences between the groups regarding the periodontal disease-associated bacteria *P. gingivalis, A. actinomycetemcomitans, T. denticola and T. forsythia*. In JIA patients, however, the levels of *P. gingivalis* and *T. forsythia* were moderately related to the plaque index, indicating a potential importance of plaque control given that these bacteria have been found to be related to periodontal disease. However, the results in the present study suggests that the studied periodontal disease-associated bacteria including *P. gingivalis* and *T. forsythia* do not contribute to neither periodontal disease, systemic inflammatory activity nor orofacial pain and jaw dysfunction, including TMJ arthritis, in JIA patients in Sweden.

There was no significant relation between subgingival levels of the investigated bacteria and the clinical TMD-variables found in the present study. These bacteria therefore do not seem to be of importance for the clinical presentation of JIA regarding musculoskeletal signs and symptoms, including signs of active TMJ arthritis. Certainly, the subjects were all free from moderate or severe periodontal disease, which may have prevented this study from observing such associations. Moderate or severe periodontal disease in children, in general, is very rare in Sweden and makes it almost impossible for a study performed in Sweden to have the power to observe such relations, should those exist. It is therefore still unknown whether higher levels of these bacteria or more severe periodontal disease affects the local (TMJ) or systemic inflammatory activity of JIA. Among the JIA patients, the plaque index was related to the gingival bleeding index, which was expected. However, this study could not find significant relations between levels of *P. gingivalis* and *T. forsythia* versus the gingival bleeding index. This may further suggest that presence and levels of these pathogens are not related to local inflammation in JIA patients to a clinically significant degree. In turn, this would support our interpretation that these bacteria do not contribute to TMD disease in these patients. Nevertheless, levels of *P. gingivalis* was related to systemic inflammatory activity, as assessed by CRP, in the JIA patients. This may indicate a potential systemic, rather than local, influence of this bacteria on JIA disease activity. On the other hand, CRP levels were low in general, with only 7% of the patients' CRP levels exceeding the normal level and then by only little. It is therefore not possible to draw any conclusions from this finding in the present study. The levels of gingival inflammation found in both JIA children and controls in this study were in accordance with data from a cross-sectional study of a random population sample of Swedish children [Norderyd et al., 2015]. The latter study showed a marked reduction of gingivitis over the last 40 years among Swedish children 10-15 year of age [Norderyd et al., 2015]. This most likely reflect the achieved improvement in personal oral hygiene routines as a result of preventive, available and regular dental care. Today, dental care is free of charge up to 23 years of age in Sweden. In other countries, or in subgroups related to socio-demographic factors, an inferior periodontal status has been found reflecting poor self-rated oral health [Paduano et al., 2018; Diamanti et al., 2021]. Indeed this should be taken into account when interpreting the results from our study. A predominant proportion of the JIA children in the studied group were on anti-rheumatic therapy with immunosuppressive medications, with the aim of suppressing systemic inflammation. This might further have had an impact in terms of reduction of gingival inflammation, especially since the combination of Methotrexate and tumor necrosis factor inhibitors has been shown to potentially decrease periodontal inflammation [Ziebolz et al., 2018]. One reason for no observed difference in the level of gingival inflammation between JIA and control might thus be the well-controlled JIA disease in the studied group. From a methodological aspect, the low scores for plaque and gingival bleeding in our study may be operator-dependent. However, the same investigator examined all subjects, which is why we consider the operator's technique to be of minor importance for the results. Conversely and to speculate, the high standard of oral hygiene and low levels of gingival inflammation found in our study might also be beneficial for the disease activity in JIA. The association between subgingival plaque levels of *P. gingivalis* and the systemic inflammatory activity in the JIA patients supports such theory. In our study, all subjects were periodontally healthy without deep periodontal pockets and none of the subjects harbored *T. denticola*. This is in accordance with results in healthy children without gingivitis aged 10 to 15 years [Mitova et al., 2018]. The high levels of periodontal health in the studied group may also explain why no associations between parotid saliva flow and levels of bacteria were found. *P. gingivalis* and *T. forsythia* were detected in a majority of the samples, both in JIA children and in healthy individuals. This was expected and in accordance with a study by Cortelli et al. [2008], indicating an increasing colonization of these species as the permanent teeth erupts. It has long been known that periodontal disease-associated pathogens ought to be seen as opportunistic pathogens that usually do not induce disease in a healthy host. However, it may affect people with a dysfunctional or suppressed immune system. Periodontal pathogens could therefore be of interest in the pathogensis of JIA but the present study could not find any relation to periodontal disease or orofacial pain and jaw function, including TMJ arthritis. Other subgingival microbial species, not studied here, may certainly still contribute.

Conclusions

In the study the presence of the two bacteria *P. gingivalis* and *T. forsythia* was associated with an increased plaque index with a higher probability of the presence of gingivitis thus increased plaque control in children with JIA is recommended for decrease the possibility of the onset of inflammatory gingival problems in term of gingivitis. The presence of the two bacteria contributes neither to systemic inflammatory activity nor to orofacial pain and jaw dysfunction, including TMJ arthritis, in patients with JIA in Sweden.

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