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Interleukin-13 Assessment in Gingival Crevicular Fluid of Patients with Periodontal Disease

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ABSTRACT

The present study holds significant potential to assess interleukin 13 (IL-13) levels in Crevicular Gingival Fluid (CGF) as a potential immunological marker for bone remodeling in subjects with periodontal disease. Thirty-nine subjects were included, with 19 diagnosed with gingivitis and 20 with periodontitis. The latter were classified following the new classification of periodontal and peri-implant diseases in stages I (6%), II (6%), III (6%), and IV (2%). Crevicular gingival fluid was meticulously collected with filter paper strips. Volume quantification was obtained with Periotron 8000® and analyzed by ELISA, ensuring the accuracy of our results. Diagnosed gingivitis patients showed a mean IL-13 level in CGF of 4.42 ± 7.5 pg/µl; in contrast, patients diagnosed in stage II of periodontitis showed higher (44.3 ± 7.5 pg/µl), followed by patients in stage III (27.5 ± 4.3 pg/µl), stage IV (25.4 ± 10.9 pg/µl) and stage I (13.8 ± 9.3 pg/µl). Due to its role in periodontitis, IL-13 might be a possible immunological marker to differentiate between bone remodeling between gingivitis and periodontitis. IL-13 might be an immunological marker playing a relevant bone role in periodontitis.

KEYWORDS: Gingivitis, Periodontitis, Interleukin-13, Bone remodeling

I. INTRODUCTION

Periodontal diseases are complex and multifactorial conditions. Their main etiological factor, dental plaque biofilms, leads to dysbiosis, causing damage to tooth-supporting tissues. These intricate interactions between the host inflammatory and immune response, their susceptibility, the supragingival and subgingival microbiota, and environmental factors can lead to the development of periodontal diseases [1-3]. This illness is highly prevalent in the Mexican population; epidemiological reports from healthcare institutions indicate that 57.5-70% of their patients present periodontal problems [4].

The high prevalence of periodontal disease among Mexicans demonstrates the necessity of implementing preventive programs; however, this is difficult due to economic reasons and the discrepancy in the definitions of different periodontal diseases [5].

Thus, it is essential to implement diagnosis approaches aiming for accurate and personalized treatment. Currently, biomarkers such as IL-13 have been proposed as indicators of the inflammatory response of periodontal tissue [6, 7]. Few studies showed that IL-13 is similar to IL-4 and IL-10 when oral tissue is inflamed and shares a biological function with IL-4 [6, 8].

IL-13 accumulation in non-oral inflamed tissues has been observed to contribute to their resolution since it inhibits the synthesis of proinflammatory cytokines. This is because IL-13 is an anti-inflammatory cytokine and maintains the Th2-type response, which promotes humoral B-cell immunity [9, 10].

Similarly, evidence shows that IL-13 decreases central proinflammatory cytokines produced by macrophages activated for bacteria, such as endotoxins, which stimulate gingival fibroblasts to synthesize integrin, proliferate and repair periodontal ligament and, as a consequence, the epithelia [11].

Finally, the inflammatory response in alveolar bone repair is activated by proinflammatory cytokines such as TNF-α, IL-1β, and IL-17, which activate osteoclastogenesis by increasing RANK (nuclear factor kB activator receptor ligand) and decreasing OPG (osteoprotegerin). However, anti-inflammatory interleukins, such as IL-13, inhibit RANKL expression and increase OPG, preventing RANK binding and its bone-resorptive activity and inhibiting osteoclastogenesis, having an anti-inflammatory and osmoregulatory function [12-14]. So, this study aims to assess interleukin 13 levels in Crevicular Gingival Fluid (CGF) as a potential marker for bone remodeling in subjects with periodontal disease.

II. MATERIAL AND METHODS

A. Study design

A case-control study was performed at the Dentistry service of the General Hospital of Zone No. 5 of IMSS. The protocol followed the ethical principles of the Declaration of Helsinki (2013), the CIOMS 2016 guidelines, and the General Health Law on Health Research. Likewise, it was accepted by the Health Research Committee No. 1701 of the Regional Hospital No. 1 of the Mexican Institute of Social Security (IMSS) in Morelos and the Bioethics Committee (17CEI0042018121). Also, it has the approval of the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) (18CI17007032).

B. Patients' enrolment

Thirty-nine subjects with no comorbidities and diagnosed with untreated gingivitis or periodontitis stages I, II, III, and IV were included. Subjects who consumed nonsteroidal anti-inflammatory drugs and antibiotics two months before study therapy, active infections, hypersensitivity, or asthma were excluded. All study subjects signed an informed consent form provided by the IMSS.

C. Clinical parameters

All patients had an oral examination at baseline. Gingivitis and periodontitis were diagnosed according to the Classification of Periodontal and Peri-implant Diseases 2017. For gingivitis, we adapted some parameters proposed by Chapple [15], such as the presence of ≥10% gingival bleeding points, proof of pocket depth ≥3 mm, gingival inflammation without loss of attachment, and the diagnostic criteria for gingival health and gingivitis induced by biofilms in clinical practice.

The Gingival or Löe & Silness index (GI) was used to evaluate the gingival status, considering the buccal, distal, mesial, and lingual or palatal dental surfaces providing a score from 0 to 3 and calculating the average of the obtained measures. The Simplified Oral Hygiene Index (SOHI) was performed only for six teeth, evaluating two variants: a) Residue index and b) Calculus index; finally, we evaluated six points of each tooth in the mouth and registered in the periodontogram. Lastly, periodontitis subjects were diagnosed according to the subclassification by stages from I to IV, where each category depends on the severity of the disease at the time of presentation and the complexity of the treatment as long as the grade gives data about biological characteristics, the rate of progression, and risk assessment [2, 15].

D. Immunological parameters

A sample of gingival crevicular fluid was taken at the baseline. A 10 mm strip of filter paper was placed inside the gingival sulcus or periodontal pocket, and then, after 30 seconds, the strip was removed and recorded. The sample volume on the filter paper strip was calculated using the Periotron® 8000; the samples were frozen at -70 °C. Afterward, samples were thawed at room temperature and eluted. Interleukin-13 levels in CGF samples were quantified using the Invitrogen commercial kit from Thermo Fisher Scientific® with a sensitivity of 4 pg/ml and a range in the standard curve of 4-500 pg/ml.

E. Statistical analysis

A database was created in Microsoft® Excel (Redmond, Washington, USA) and then analyzed using the software IBM SPSS® version 25 (Chicago, USA). Data were summarized as means, standard deviations (SD), and relative frequencies for each parameter. Significant testing was performed using the T-Student(α=0.95) test and Analysis of Variance (ANOVA), also a chi square test was done using risk estimation.

III. RESULTS AND DISCUSSION

This study analyzed 39 subjects, from which 53.85 % were male and 46.15 % female with an age of 36.30 ± 12.33 years old (average ± SD). 19 subjects were diagnosed with gingivitis with intact periodontium, and 20 were diagnosed with periodontitis classified by stage. Table 1 shows the correlation between the diagnosed disease and SOHI classification of the analyzed subjects.

Table 1. SOHI Classification of the Analyzed Subjects by Diagnosed Disease

Periodontal Disease	*SOHI*			
	Deficient	*Regular*	*Good*	*Total*
Gingivitis	11	5	2	18
SIP	4	2	0	6

SIIP	6	0	0	6
SIIIP	4	2	0	6
SIVP	1	0	0	1
Total	26	9	2	37*

*: SOHI was not determined for 2 subjects. SIP: Stage I Periodontitis. SIIP: Stage II Periodontitis. SIIIP: Stage III Periodontitis. SIVP: Stage IV Periodontitis.

Intergroup clinical parameters analysis from the intact periodontum gingivitis subjects and the periodontitis classified by stage patients is shown in Table 2 (values are presented as average ± SD).

Table 2. Intergrupal Clinical Parameters

Periodontal disease	PD (mm)	LOI (mm)	% LOI	GI
Gingivitis	2.58±0.60	ND	ND	1.71±0.74
SIP	3.67±0.51	4.00±0.00	30.18±16.40	2.35±0.79
SIIP	4.00±0.00	5.00±0.00	22.80±17.38	2.19±0.73
SIIIP	5.80±0.75	5.80±1.63	28.10±19.81	2.27± .63
SIVP	4.50±0.70	9.50±2.12	57.65±34.43	1.05±1.48

PD: Pocket Deep; LOI: Lost of insertion; GI: Gingival index; SIP: Stage I Periodontitis. SIIP: Stage II Periodontitis. SIIIP: Stage III Periodontitis. SIVP: Stage IV Periodontitis; ND: Non determined.

Periodontal disease was classified as focal or generalized. To establish its extension, we classified it as focal intact periodontum gingivitis if there were present 10 to 30 % bleeding sites or generalized intact periodontum gingivitis if there were > 31 % bleeding sites. In the case of periodontitis, we based the classification on analyzing the clinical loss of attachment in localized if there was ≤ 30 % and generalized if there was > 31 % of affected sites (Table 3).

Table 3. Periodontal Diseases Classification by Extension

Periodontal disease	Focal	Generalized
Gingivitis	11	8
SIP	3	3
SIIP	5	1
SIIIP	4	2
SIVP	0	2
Total	23	16

SIP: Stage I Periodontitis. SIIP: Stage II Periodontitis. SIIIP: Stage III Periodontitis. SIVP: Stage IV Periodontitis

Regarding the immunological parameters, we analyzed CGF volume, total IL-13, IL-13 concentration and frequency of bleeding points with a T-Student$_{(\alpha=0.95)}$ test between gingivitis and periodontitis subjects. The results are shown in figure 1. We found that IL-13 concentration, total IL-13 and intact periodontium gingivitis subjects showed statistical difference with a very high significance ($p<0.001$), while CGF volume was no statistically different among both groups.

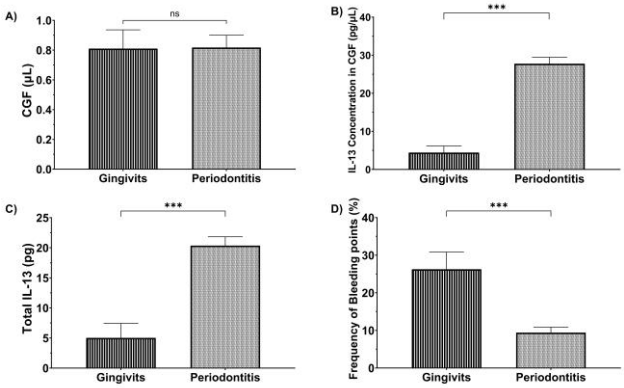

Figure 1. Comparison of immunological parameters among gingivitis and periodontitis subjects with a T-Student test (mean ± SEM plotted). A) CGF volume; B) IL-13 concentration in CGF; C) Total IL-13; D) Frequency of bleeding points. ns: non-significant; *: very high significance ($p<0.001$); SEM: Standard Error of the Mean.**

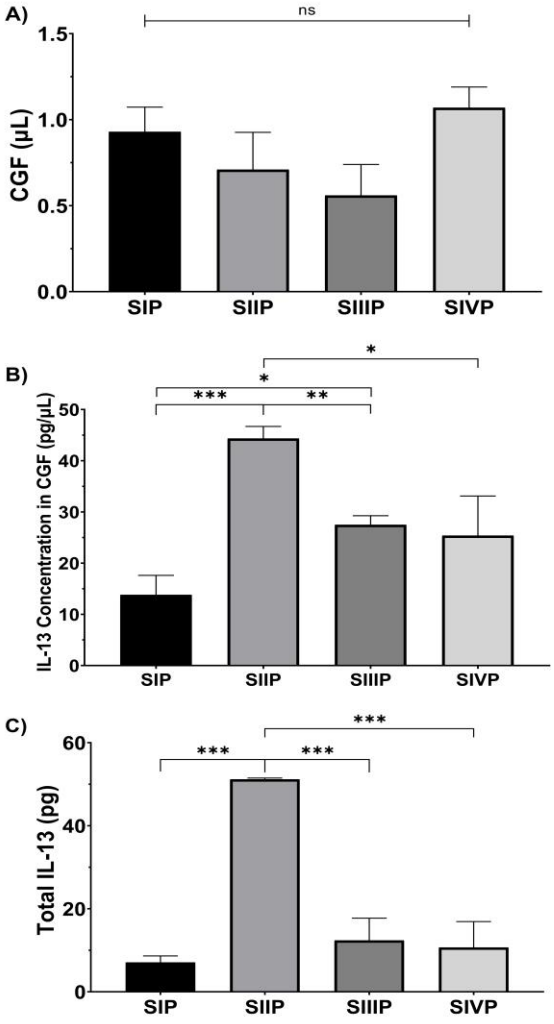

Figure 2. ANOVA results for the comparison among the periodontitis groups (Mean ± SEM plotted). A) CGF volumen; B) IL-13 concentration in CGF; C) Total IL-13.

SIP: Stage I Periodontitis; SIIP: Stage II Periodontitis; SIIIP: Stage III Periodontitis; SIVP: Stage IV Periodontitis; *: significance ($p<0.05$); **: high significance ($p<0.01$); ***: very high significance ($p<0.001$); SEM: Standard Error of the Mean.

Figure 2 shows the results from ANOVA test performed on periodontitis subjects classified by stage. A Tukey post-hoc multiple comparison test was made where a statistically significant difference was found ($p<0.05$) to determine which groups are specifically different. There was no difference for CGF volume, but total IL-13 and IL-13 concentration did present a difference with very high significance ($p<0.001$), periodontitis stage II group was the group who showed to be the most different among the others.

Risk estimation (OR, Odds Ratio) was calculated by analyzing the SOHI in subjects with periodontal disease. First, we converted SOHI into a dichotomous variable by grouping good and regular categories at a unique level. The chi-square test yielded a value of $p=0.414$, indicating no correlation between the SOHI index and periodontal disease. Supragingival and subgingival dental plaque biofilm is relevant in the onset of gingivitis and periodontitis because of the dysbiosis in periodontium bacteria [16, 17]. Dysbiosis initiates inflammation and the host response, causing epithelium damage, an increment in vascular permeability, high production of inflammatory molecules, and gingival edema [17, 18]. Extravasated plasma seeps into the gingival sulcus and increases the crevicular fluid volume, expressed as an inflammatory exudate [19, 20]. Numerous inflammatory cells close to the alveolar bone activate osteoclasts and bone resorption, causing periodontal damage and loss of teeth [16, 17]. Crevicular fluid analysis allows the assessment of immunological biomarkers that reflect the interaction between the host and the periodontopathogenic bacteria during the different stages of periodontal disease and, thus, serves as an early diagnostic aid applicable in clinical practice [19].

Applying the criteria of the 2017 Classification of Periodontal Diseases for periodontal status assessment allows the evaluation of clinical parameters using gingival and periodontal signs, which are related to each patient's periodontal status and give an initial overview of the disease and the possible relationship between tissue destruction [2].

This study brings insights into the relationship between CGF volumes and the inflammatory process of gingivitis and periodontitis. Our results, which diverge from previous studies [7], underscore the importance of the applied methodology and the sensitivity of the ELISA test. We found a mean of 0.53 (SD±0.22) µl for gingivitis and 0.81 (SD± 0.33) µl for periodontitis. Moreover, our pioneering results in CGF levels by stages of periodontitis fill a gap in the literature where such data was previously unrecorded. Therefore, this study provides significant and unique information for studying periodontal diseases.

Amidst the complex landscape of periodontal diseases, the gingival crevicular fluid volume is a crucial indicator of disease progression. In this context, IL-13 emerges as a promising immunological biomarker, offering potential applications in the diagnosis, treatment, and prognosis of gingivitis and periodontitis across their various stages. This finding holds significant promise in the context of periodontal disease, as it underscores its importance for tissue homeostasis by stimulating macrophages to activate gingival fibroblasts for the production of type I collagen, regulating and boosting the production of TGF-β and directly stimulating fibroblasts in the production of collagen while inhibiting its destruction [19, 21]. IL-13's role in bone regulation is particularly noteworthy, as it suggests that IL-13 levels could be used to monitor bone health and predict the progression of periodontal diseases.

The present study revealed significant findings on the total IL-13 concentration in subjects with gingivitis and periodontitis. We found that the IL-13 concentration in subjects with gingivitis was 4.42 ± 7.50 pg/µL, and in subjects with periodontitis stage I was 13.81 ± 9.30 pg/µL, stage II 44.36 ± 5.70 pg/µL, stage III 27.50 ± 4.30 pg/µL, stage IV 25.40 ± 10.90 pg/µL. These values may be attributed to the ability of IL-13 to maintain a Th2-type response, mediating the absence of anti-inflammatory interleukins and promoting the activation of cells involved in tissue repair. These outcomes align with the findings of [19], where the patients diagnosed with chronic periodontitis presented an IL-13 mean of 0.74 ± 0.12 pg/µl at the beginning of the study, and three months later, the mean value increased to 4.63 ± 0.47 pg/µl. These results suggest the increase of IL-13 as a possible stage of bone regeneration [11].

Our study breaks new ground by reporting the mean concentration of IL-13 in the crevicular gingival fluid. We observed that subjects with gingivitis have a mean of 4.42 ± 7. 50 pg/µL, which might be related to the state of acute gingivitis mediated by proinflammatory cytokines such as IL-1β, IL-8, among other interleukins of Th1 profile; therefore, the IL-13 osmoregulatory profile has minimal participation in this state. There is not yet damage to bone tissue where it has greater participation. On the other hand, for periodontitis, we found an average of 27.77 ± 7.55 pg/µL; in this case, the total concentration of this interleukin is only reported in aggressive periodontitis and chronic periodontitis (classification 1999).

The current information regarding IL-13 concentration in periodontal diseases is scarce. A study showed that in an in-vitro culture of lymphocytes from patients with aggressive periodontitis and genotype -34AA and -509TT in IL-4 (whose receptor and functions are shared with IL-13), massive levels of IL-13 were found (509.67 pg/ml) without the participation of the associated microbiota. However, we

must consider the involvement of other cell lines, the type of patients studied, and the sample volumes obtained, among other related factors [22].

The relevance of current work resides in L-13 volume determination in patients with different stages of periodontitis. A possible explanation for IL-13 presence in these pathologies might be with the bone regulation activity, as it is known periodontitis implies bone damage caused mainly by the presence of RANKL and its osteoclastogenic activity, which is secreted chiefly by interleukins of the Th1 profile. When these interleukins are present, tissues try to return to their natural homeostasis; this implies the presence of antagonists of the proinflammatory cytokines, such as IL-13. As we know, in stage I of periodontitis, damage to the bone is present, although in a lower percentage than in later stages; it is here where IL-13 can begin its bone regulatory activity by secreting OPG to avoid further bone destruction, while in stage II the IL-13 volume was higher than in the other stages, this might be due to a more significant attempt to recover the metabolic balance of the bone and avoid its resorption. Lastly, stage III and IV subjects presented decreased IL-13 volumes, and all the clinical signs of their stages were observed, which may indicate that this interleukin was diminished in its bone regulatory activity.

Given the data obtained about clinical and immunological parameters, IL-13 can be considered an immunological biomarker of periodontal disease since low or null levels of IL-13 were found in subjects with gingivitis and presented relevant clinical data of inflammation. Therefore, we can infer that IL-13 decreases in the presence of proinflammatory interleukins and that there is still no damage to bone tissue. The highest levels of IL-13 were found in patients with periodontitis, which indicates that in stage II, there may be an attempt to recover the state of bone homeostasis. New studies suggest anti-inflammatory cytokines such as IL-13 can modify the microenvironment and promote bone homeostasis, inhibiting osteoblast proliferation by producing RANKL. It also can secrete OPG, increase collagen secretion and mineralization, and stimulate macrophages for successful bone healing [11, 23, 24].

IV. CONCLUSION

According to the results obtained in the present work, IL-13 can be proposed as a bone regulation biomarker that allows differentiation between the clinical entities of periodontitis and gingivitis since alterations of this interleukin were observed in the different diseases and their stages; however, more trials in a larger population are needed better to evaluate the impact of the disease on this biomarker and to understand its role.

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