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Levels of IL-23/IL-17 Axis in Plasma and Gingival Tissue of Periodontitis Patients According to the New Classification

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Abstract: Background: Periodontitis (P) is a chronic inflammatory disease characterized by the destruction of periodontium support tissue generated by different immuno-inflammatory mechanisms, including the RANK/RANKL/OPG and the IL-23/IL-17 axis. Methods: The study was performed with healthy subjects (HS) and patients with periodontitis. Plasma samples were obtained from peripheral blood and the gingival tissue (GT) during periodontal surgery. The ELISA technique was used to evaluate the levels of IL-23, IL-17A, IL-23R, and IL-17RA. Results: In the plasma, a significant decrease in IL-17A was observed in patients with periodontitis than HS. In the GT, IL-23, IL-17A, and IL-17RA levels were increased in periodontitis patients; on the contrary, IL-23R levels were decreased in periodontitis patients when compared with HS. Finally, several positive correlations were found: soluble IL-17RA (sIL-17RA) levels in plasma between the percentage of radiographic bone loss (RBL%), and IL-23 with IL-17A in gingival tissue. Conclusions: The detection of the IL-23/IL-17A axis in gingival tissue and plasma provides us with more information on the behavior of this axis in a localized way in the periodontal microenvironment, in contrast to the systemic levels evaluated according to the new classification of periodontitis.

Keywords: Interleukin-23; Interleukin-17; Interleukin-23 receptor; Interleukin-17 receptor; periodontitis

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1. Introduction

Periodontitis is caused by multiple risk factors such as bacterial dysbiosis, destructive host immune responses, and environmental factors such as smoking [1]. It is distinguished by an immuno-inflammatory solid response characterized by gingival inflammation, periodontal pockets (sites with deep probing depths), attachment loss, and radiographic bone loss [1,2]. However, dysbiosis is not sufficient to induce loss of attachment or erosion of the alveolar bone [3]. In this context, dendritic cells and macrophages stimulated by periodontal pathogenic bacteria produce IL-23 which plays an important role in the innate immune responses to bacterial and fungal infections diseases [4,5]. IL-23 binds to IL-23R which is expressed in several cells such as macrophages, dendritic cells, and natural killer (NK) cells, but principally on Th17 cells [6]. After binding of IL-23 to IL-23R, Th17 cells become activated and release IL-17A, IL-17F, IL-6, IL-22, and tumor necrosis factor α (TNF-α) [6,7], and the receptor activator of the NF-κB ligand (RANKL) [8]. IL-17 activates cells such as fibroblasts through the IL-17A receptor (IL-17RA/RC) and induces the release of RANKL [9]. RANKL released by fibroblasts and Th17 cells binds to RANK

expressed on osteoclast precursor and induces their maturation to initiate bone destruction in periodontitis [9].

Significantly, IL-23R and IL-17RA can be in soluble form (sIL-23R and sIL-17RA) [10]. IL-23 binds to IL-23R and forms a complex (IL-23-IL-23R), acting as an inhibitor or activator of Th17 cell signaling [10,11] while sIL-17RA can function as a blocker of IL-17A signaling [12].

IL-23/IL-17 axis in periodontitis has been studied in different biological samples. Regarding IL-23 in gingival crevicular fluid (CGF), high concentrations have been reported in patients with periodontitis [13,14], as well as in saliva [15]. Contrary to Sadeghi R et al., who found decreased IL-23 when compared to healthy subjects (HS) [16]. On the other hand, some study groups did not observe significant differences in IL-23 between HS and periodontitis in GCF samples [17,18]. Other study groups demonstrated that patients with periodontitis have higher levels of IL-23 compared in serum and plasma [19,20]. Regarding IL-17 concentrations, elevated concentrations have been reported in CGF samples from patients with periodontitis compared to HS [17,21–23]. Elevated concentrations of IL-17A were reported in serum, plasma, and saliva samples in patients with periodontitis compared to HS [13–15,24,25]. Contrarily, Ozçaka O et al., found higher IL-17 in the saliva of HS compared to patients with periodontitis [26], but in other study however, in another study, there were no significant differences [27].

In gingival tissue samples, few working groups have evaluated the IL-23/IL-17 axis, of which IL-17 is elevated in patients with periodontitis compared to healthy subjects [21,28]. However, Takahashi K et al. only detected IL-17A in 10 of 16 gingival tissue samples from patients with periodontitis [29]. Ohyama H et al., reported higher IL-23 and IL-23R mRNA expression in early and advanced periodontal lesions compared to biopsies from healthy sites of periodontitis [30].

Regarding the receptors of IL-23R and IL-17RA, our study group have described that IL-23R is diminished and IL-17RA increased in gingival tissue from chronic and aggressive periodontitis patients [31]. Based on studies conducted on gingival tissue of the IL-23/IL-17 axis in periodontitis patients diagnosed according to the 1999 classification, we hypothesized that the molecules of the IL-23/IL-17A axis are increased in the gingival tissue in periodontitis coupled with the progression and severity of periodontitis based on the classification of periodontal disease (2018).

2. Materials and Methods

2.1. Ethical Approval and Informed Consent

This study was submitted and approved by the Ethics and Research Committees of Guadalajara University, and the Regulations of the General Health Law with the approval number (CI-08020). Additionally, the study was conducted according to the regulations of the World Medical Association Declaration of Helsinki 2013.

2.2. Study Subjects

Sixty-two subjects were enrolled to participate in the Periodontics Clinic of the University of Guadalajara from 2019 to 2020.

Inclusion criteria: Patients who showed typical characteristics of periodontitis and periodontally healthy. All the included subjects had not received periodontal therapy, medicaments such as antibiotics, anti-inflammatory drugs, or immunomodulators in the six months prior to the study.

Exclusion criteria: Smoking subjects, pregnant women, subjects who were under prophylactic antibiotic or dental treatment, those who took drugs that affect the gingiva, and subjects who presented a systemic disease were excluded from the study.

2.3. Periodontal Clinical Parameters

A clinical examination was performed on six sites per tooth of all existing dental organs of all participants with a Hu Friedy periodontal probe of 15 mm long and 0.5 mm

in diameter (University of North Carolina UNC-15 Hu Friedy, Chicago, IL, USA), and the results were averaged [32,33]. The probing depth (PD), clinical attachment loss (CAL), percentage of bleeding on probing (BoP%), and percentage of radiographic bone loss RBL% were measured. The percentage of radiographic bone loss RBL% was assessed in relation to the root size of the most affected tooth. Likewise, data was collected from the specific area from which the gingival tissue was obtained.

All the HS did not present gingival inflammation and radiographic bone erosion. All patients with periodontitis were diagnosed according to the classification of periodontal diseases (2018) [34]. The diagnosis and classification of periodontitis were carried out by two calibrated specialists from the Periodontics Clinic of the University of Guadalajara.

2.4. Study Groups

Group of healthy subjects: This group consisted of 28 HS, (6 male, and 22 female), with a mean age of 37.26 $\pm$ 1.82 who were treated at the Periodontics Clinic for cosmetic surgery or crown lengthening. The group of healthy subjects showed a PD $\leq$ 2, CAL $\leq$ 1, BoP% < 10%, and no evidence of RBL%.

Group of periodontitis patients: This group consisted of 34 patients, (8 male, and 26 female); with a mean age of 40.5 $\pm$ 2.06, who presented periodontal pockets (CAL $\geq$ 5 mm and PD $\geq$ 4 mm), BoP% $\geq$ 10%, and RBL%. Patients with periodontal stage III and IV were included because, according to periodontal treatment, these patients did require surgery.

2.5. Plasma Sample Collection

Peripheral blood was obtained from all study subjects by venous puncture in a tube with EDTA and then centrifuged for 10 min at 700$\times$ *g* at room temperature. Next, the plasma was collected and immediately stored at $-$80 °C until ELISA assay.

2.6. Gingival Tissue Collection and Protein Extraction

Gingival tissue collection from HS and periodontitis patients were performed during aesthetic surgery or crown lengthening, and during the surgical phase of treatment, respectively. Sections from each tissue were collected, weighed, and placed in a microtube with 300 µl of PBS buffer. The microtubes were then placed in ice (4 °C), transported to the laboratory, and stored in an ultrafreezer at $-$80 °C until analysis.

To obtain total proteins, the samples were thawed at room temperature, subjected to the vapors of liquid nitrogen to crystallize them, and then crushed by compression. The triturated gingival tissue was immersed in 300 µL of RIPA buffer (Sigma, River Edge, NJ, USA) plus protease inhibitor (Complete, Roche Diagnostic GmbH, Risch, Switzerland) for 20 min at 4 °C. The homogenate was centrifuged at 12,300$\times$ *g* for 10 min and the supernatants with the total proteins were collected and stored at $-$80 °C until the quantification of IL-23, IL-17A, IL-23R, and IL-17RA by the ELISA method.

The quantification of total proteins was performed by the Bradford Coomassie Protein Assay Kit method (Thermo Fisher Scientific, Waltham, MA, USA). It was read on a spectrophotometer at 590 nm. The total protein concentration was obtained in mg/mL.

2.7. Enzyme-Linked Immunosorbent Assay (ELISA)

The plasma and gingival tissue samples were added in triplicate to the wells of microtiter plates to determine the concentrations of human IL-23, IL-17A, IL-23R, and IL-17RA using DuoSet® ELISA Kits (R&D Systems, Minneapolis, MN, USA). The absorbance of each well was read at 450 nm in a microplate spectrophotometer (Poweam Medical Systems, Co., Nanjing, China). The IL-23, IL-17A, IL-23R, and IL-17RA levels were calculated from the standard curves included in each assay. The levels in the plasma were expressed as pg/m, and in gingival tissue expressed as pg/mg of gingival tissue. When performing

the ELISA technique, the concentrations are shown in pg/mL; thus, the picograms of each molecule were adjusted according to the tissue weight using the following formula:

$$\frac{pg/mL\ of\ citokyne\ or\ receptor\ by\ ELISA}{mg/mL\ of\ gingival\ tissue} = pg/m \quad (1)$$

2.8. Statistical Analysis

For a small sample size, the data distribution was evaluated using the Shapiro–Wilk test. The data were abnormally distributed therefore, a nonparametric Mann–Whitney U test was used to compare the median differences between the study groups. A Chi-squared test was used to compare the sex. The correlation of the clinical findings and the levels of IL-23, IL-23R, IL-17A, and IL-17RA in the plasma and gingival tissues were evaluated by Spearman rank correlation coefficient. A value of $p \leq 0.05$ was considered significant. These results were analyzed using SPSS software version 25.0 (Chicago, IL, USA). Finally, the effect size and power of the study were analyzed with the G * P3.1 software.

3. Results

3.1. Demographic Characteristics and Clinical Parameters

The female gender dominated in both study groups; in terms of age, patients with periodontitis were older than healthy subjects. Regarding the periodontal characteristics, these were measured in all the areas of the teeth present and averaged, likewise was measured the exact value of the area where the gingival tissue was obtained. Patients with periodontitis presented a significant increase in PD, CAL, and BoP% in general measurements, as well as in the area of gingival tissue collected. It is worth mentioning that HS do not present RBL%, however, patients with periodontitis showed bone loss above 50% (Table 1).

Table 1. Demographic characteristics and clinical parameters.

	HS	P
Gender M/F	6/22	8/26
Age (years)	37.26 ± 1.82	40.85 ± 2.06 *
PD (mm)	2.14 ± 0.13	4.87 ± 0.4 *
CAL (mm)	1.02 ± 0.2	5.24 ± 0.49 *
BoP%	0.52 ± 0.52	22.65 ± 6.77 *
RBL%	-	60.55 ± 5.18
PD GT (mm)	2.31 ± 0.11	5.21 ± 0.44 *
CAL GT (mm)	1.07 ± 0.25	5.47 ± 0.46 *
BoP GT%	1.38 ± 1.38	24.47 ± 8.56
Stage III	-	26
Stage IV	-	8
Grade A	-	17
Grade B	-	11
Grade C	-	6

The results are expressed as mean and standard error or percentage. HS: Healthy Subjects, P: Periodontitis, M: Male, F = Female, PD: Probing depth, CAL: Clinical Attachment loss, BoP%: Bleeding of Probing percentage, RBL%: Percentage of Radiographic Bone Loss. GT: site of gingival tissue was obtained. * Significant difference between HS and P. A $p \leq 0.05$ was considered as significant.

3.2. Levels of IL-23/IL-17A Axis and Soluble Receptors in Plasma

No significant differences were observed in IL-23 and sIL-23R between the group of patients with periodontitis and HS (Figure 1a,b). A significant increase in IL-17A was observed in HS than periodontitis group (Figure 1c). Additionally, sIL-17RA was similar between healthy subjects and patients with periodontitis (Figure 1d).

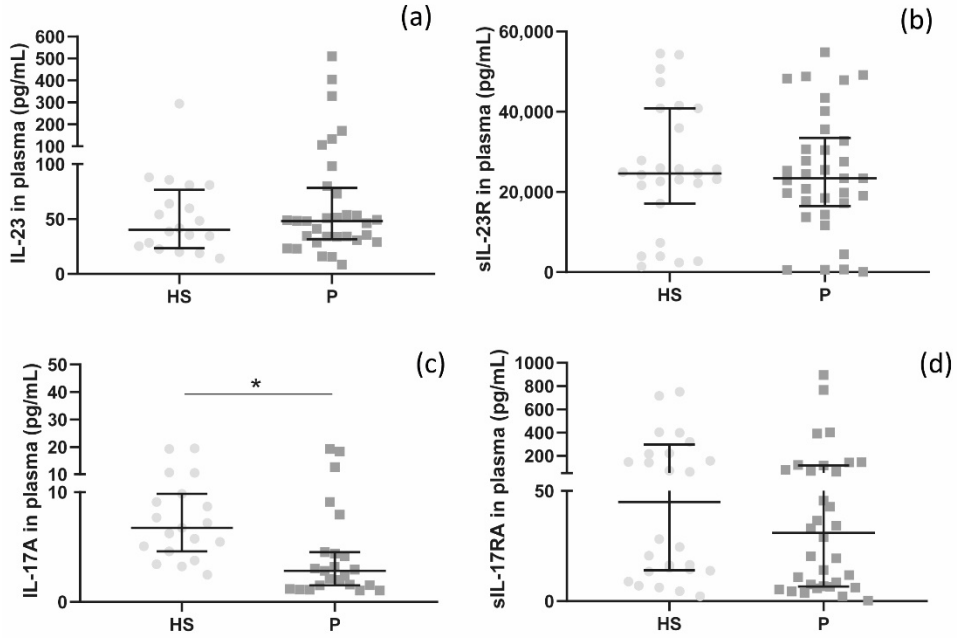

Figure 1. IL-23, IL-17A, sIL-23R, and sIL-17RA levels in plasma. plasma levels of IL-23 (**a**), sIL-23R (**b**), IL-17A (**c**), and sIL-17RA (**d**) from healthy subjects (HS) and periodontitis patients (P) were detected by ELISA and are expressed as pg/mL. The results are shown as median and interquartile ranges. * A p-value ≤ 0.05 was considered significant.

3.3. Levels of IL-23/IL-17A Axis and Receptors in the Gingival Tissue

In this study, we found an increase in IL-23 in the gingival tissue of patients with periodontitis compared with HS (Figure 2a). On the other hand, IL-23R levels in the gingival tissue were found to be higher in healthy subjects compared with patients with periodontitis (Figure 2b).

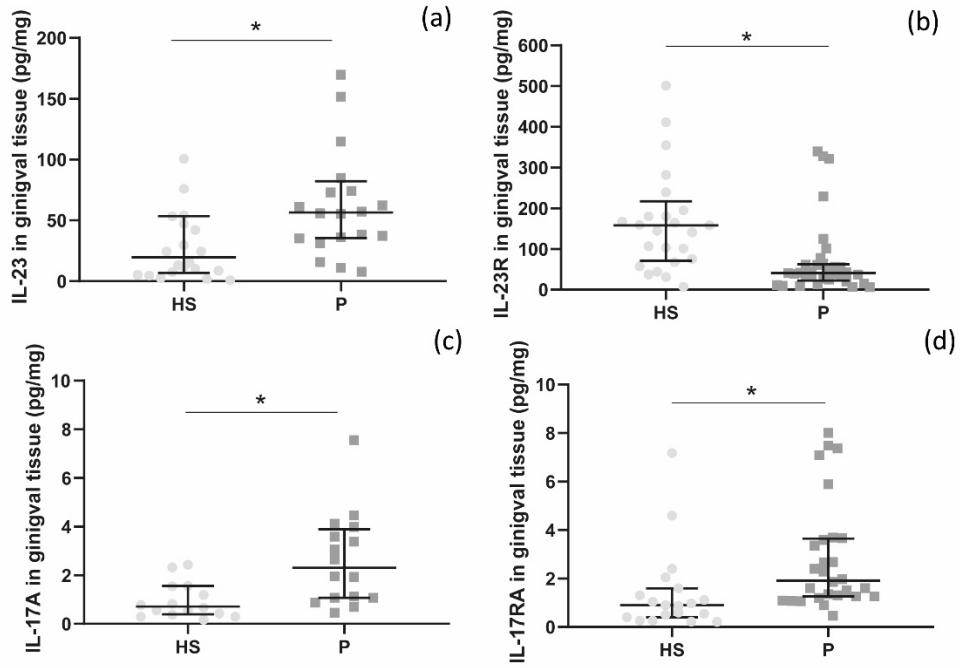

Figure 2. Levels of IL-23, IL-17A, IL-23R, and IL-17RA in gingival tissue. gingival tissue levels of IL-23 (**a**), IL-23R (**b**), IL-17A (**c**), and IL-17RA (**d**) from healthy subjects (HS) and periodontitis patients (P) which were detected by ELISA and are expressed as pg for each mg of gingival tissue. The results are shown as median and interquartile ranges. * A p-value ≤ 0.05 was considered significant.

Regarding IL-17A in gingival tissue, it was found to be elevated in patients with periodontitis compared with HS (Figure 2c). Similarly, IL-17RA in gingival tissue was found elevated in periodontitis patients compared with HS (Figure 2d).

3.4. Correlation between IL-23, IL-17A, IL-23R, and IL-17RA with Clinical Parameters in Plasma and Gingival Tissue

A Spearman correlation test was implemented in IL-23, IL-17A, IL-23R, and IL-17RA levels between plasma and gingival tissue and the clinical parameters. Only a positive correlation was observed in plasma molecules: IL-17RA vs. IL-23R r = 0.381 p = 0.003. Regarding the clinical characteristics, two positive correlations were found between IL-17RA vs. RBL % r = 0.575 p = 0.010 and PS vs. CAL r = 0.855 p = 0.000.

Regarding the gingival tissue, several positive correlations were observed: IL-17A-GT vs. IL-23-GT r = 0.592 p = 0.000; IL-23-GT vs. IL-17RA-GT r = 0.683 p = 0.000; IL-17A-GT vs. IL-17RA-GT r = 0.448 p = 0.013. As well as negative correlation: IL-23-GT vs. IL-23R-GT r = −0.329 p = 0.033. In the same way, correlations were found with the specific clinical parameters of the gingival tissue obtaining areas: IL-23R-GT vs. PS-GT r = −0.514 p = 0.000; IL-23R-GT vs. CAL-GT r = −0.508 p = 0.000; IL-17A-GT vs. PS-GT r = 0.462 p = 0.030; IL-17A-GT vs. CAL-GT r = 0.469 p = 0.037; IL-17RA-GT vs. CAL-GT r = 0.371 p = 0.024, and PS-GT vs. CAL-GT r = 0.877 p = 0.000.

Finally, we made a correlation of the IL-23/IL-17 axes molecules between plasma and GT as well as with the clinical characteristics obtained. We found both positive and negative correlations: IL-17A vs. IL-17A-GT r = −0.592 p = 0.001; IL-23R-GT vs. PS r vs. = −0.477 p = 0.000; IL-23R-GT vs. CAL r = −0.480 p = 0.001; IL-17RA-GT vs. CAL r = 0.320 p = 0.047; PS vs. PS-GT r = 0.895 p = 0.000; PS CAL-GT r = 0.808 p = 0.000; CAL vs. PS-GT r = 0.821 p = 0.000; CAL vs. CAL-TG r = 0.944 p = 0.000; BoP % vs. PS-GT r = 0.501 p = 0.004, and BoP % vs. BoP %-GT r = 0.891 p = 0.000 (Figure 3).

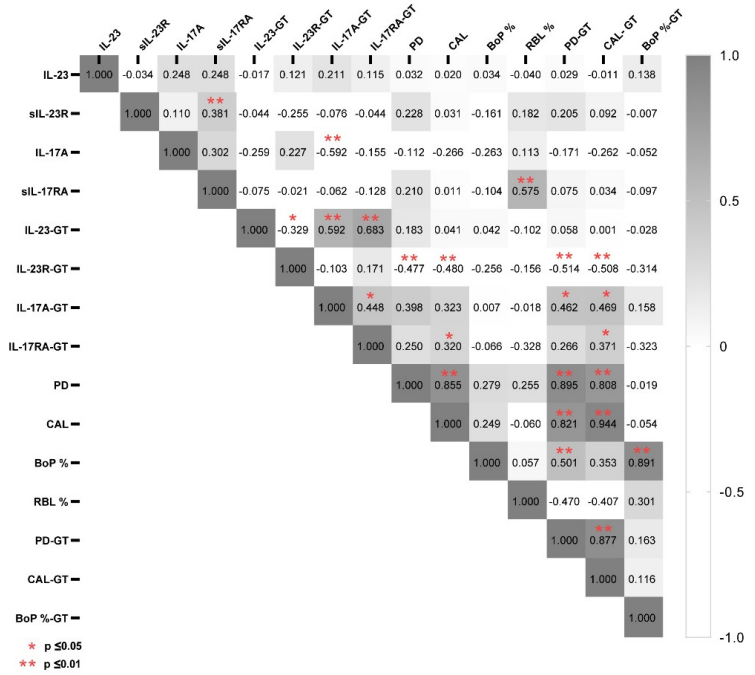

Figure 3. Correlation between the IL-23/IL-17A axis molecules and IL-23R IL-17RA receptors with clinical parameters in plasma and gingival tissue were analyzed using the Spearman correlation test. PD: probing depth, CAL: clinical attachment loss, BoP%: bleeding on probing percentage, RBL%: percentage of radiographic bone loss in plasma and (GT): gingival tissue values. * $p \leq 0.05$, ** $p \leq 0.01$.

3.5. Power and Effect Size

A post hoc exploration of the effect size and power of the study were analyzed with the G * P3.1 software, considering a unilateral hypothesis with $\alpha = 0.05$. Only the sIL-23R and IL-23-GT showed a poor effect size and power (Table 2).

Table 2. Power and effect size of IL-23/IL-17 axes in periodontitis.

	IL-23	sIL-23R	IL-17A	sIL-17RA	IL-23-GT	IL-23R-GT	IL-17A-GT	IL-17RA-GT
Power	0.99 *	0.098	1 *	0.99 *	0.43	1 *	0.99 *	1 *
Effect size	1.04 *	0.075	2.02 *	0.89 *	0.37	2.61 *	1.46 *	2.55 *

GT: site of gingival tissue was obtained. * power $\geq$ 80 or effect size $\geq$ 0.5.

4. Discussion

Interactions between various cells and molecules in the immune system of the host's periodontal tissue are necessary, such as the IL-23/IL-17A axis, which can mediate the destruction of the periodontium. In this study, we expected to find an increase in the IL-23/IL-17A axis in the plasma and gingival tissue of patients with periodontitis. However, this behaviour was not observed in all the molecules of the IL-23/IL-17A axis, according to the classification of periodontal disease (2018).

Regarding IL-23 and sIL-23R in plasma, a significant difference was not observed between healthy subjects and patients with periodontitis. In this sense, the power and size of the effect for sIL-23R were not sufficient to establish an absolute result, so it is pertinent to increase the size of the samples. Regarding IL-23 in plasma, it is possible that in periodontitis patients this citokyne are diminished in the chornic fase (stage III and IV) of this disease, getting similar levels of IL-23 as healthy subjects. This phenom can be explained by the hyphotesis "Inflammation-Mediated Polymicrobial-Emergenceand Dysbiotic-Exacerbation"(IMPEDE), this hypothesis states that in the periodontitis cours a cycle where the inflammation resolution can restore the periodontal health afther a treatment [35]. It is important to say that the periodontitis patients from this study have non-surgical treatment before participating. Likewise, other studies have evaluated somes citokynes before and after treatment, and have shown that some citokyne levels decreased after non-surgical treatment (mechanical removal of dental plaque) and some periodontitis patients can regulate the production of proimflamatory citokynes managing to maintain similar levels similarly to healthy subjects [19,22,36].

Contrarily, an increase in IL-23 was observed only in the gingival tissue of patients with periodontitis compared to healthy subjects, according to Ohyama H. et al., that evaluated this cytokine in gingival tissue by immunohistochemistry and mRNA expression via PCR [30]. It is possible that the evaluation of cytokynes is better or more exactly in the specific tissue that by systemic way, because is the place where the inflammation is occurring and these molecules (IL-23/IL-17 axis) can be expressed according to the stimulus on the periodontum or by the periodontal stage and grade as proposing van Dick et al. [35].

In the present study, significant differences were not observed in sIL-23R in plasma samples. However, a decrease in IL-23R in the gingival tissue of periodontitis patients was demonstrated. In this sense, it is known that IL-23 can regulate the expression of IL-23R [37]. Considering that IL-23 in gingival tissue is increased in the periodontitis patients in this study, we expected to find an increase in IL-23R. In addition to this finding, the IL-23 increase and IL-23R decrease in gingival tissue are reflected in a negative correlation. In this regard, it has been observed that ADAM17 is elevated in the periodontal tissue of periodontitis patients [38,39], and ADAM17 has been shown to cleave IL-23R expressed on the cell membrane [11]. This mechanism likely partly explains the decreased expression of IL-23R that was found in the gingival tissue of periodontitis patients, which could be since that there are multiple protein isoforms of IL-23R, including soluble isoforms [11] that could not be detected by the ELISA method. It would be interesting to analyze IL-23R by western blot to identify possible isoforms of IL-23R and then to characterize these isoforms

by mass spectrometric and grades of glycosylation of IL-23R [40], due to the fact that some IL-23R isoforms have been described in Bowel's disease [41].

On the other hand, in plasma samples, there is a decrease in IL-17A in patients with periodontitis, similar to that reported by some authors regarding GCF [42] and plasma [22]. In contrast, other authors have described an increment in the concentration of IL-17A in different biological fluid samples from periodontitis patients [17,18,26], while others still failed to detect this cytokine in patients with periodontitis [12,13]. However, IL-17A is a cytokine highly studied in inflammatory and autoimmune diseases such as Sjögren's syndrome and rheumatoid arthritis, among others [43–46]. In this sense, Ridgley LA. et al. [47] propose that several cytokines, such as IL-17A, are inversely proportional to the course and chronicity of rheumatoid arthritis. In addition, an increase in IL-17A was observed in the preclinical phase, and this cytokine decreases as the chronicity of RA enhances [47]. Although, periodontal disease affects the bone and periodontal tissue and is known to have a similarity to RA [48]. IL-17A in periodontitis may exhibit behavior similar to what Ridgley LA et al. propose in rheumatoid arthritis.

Contrary to plasma, in gingival tissue samples an increase in IL-17A was observed in periodontitis patients than HS, which coincides with that reported by Johnson RB et al., and Ruiz AC et al., in gingival tissue [28,31] as well as by Vernal R et al., in gingival culture supernatant [21]. This increase in IL-17A can be attributed to the gingival microenvironment generated by the severity of periodontitis, since in this study all patients were between periodontal stages III and IV, being the most advanced of periodontitis [1]. This finding can apply the Ridgley observation in some molecules, such as IL-17A that are overexpressed according to the severity and chronicity of rheumatoid arthritis [47].

Regarding sIL-17RA in plasma, differences between HS and periodontitis patients were not found. An increase in sIL-17RA was expected in periodontitis because in a previous study, this receptor was observed increased in the gingival tissue of patients with periodontitis [31], sowe considered that sIL-17RA could be elevated in plasma because several soluble isoforms of sIL-17RA can be secreted as a result of alternative splicing [12]. In addition, an increase in IL-17RA has been observed in other pathologies [49–51].

On the other hand, sIL-17RA positively correlated with the RBL%, which is a parameter that indicates the periodontal grade (severity); in this regard, the inhibitory effect of some IL-17A soluble receptors on IL-17A in vitro has been demonstrated [52,53]. The study of the sIL-17RA expression isoforms in periodontitis could elucidate the role that these molecules play in bone resorption in this disease.

Regarding IL-17RA in gingival tissue, an increase was observed in patients with periodontitis as reported by previous studies in patients with chronic and aggressive periodontitis [31]. It has been shown that there is an increase in RANKL produced by fibroblasts under the stimulus of IL-17A when binding to its receptor [54]. Therefore, the enhanced levels of IL-17A [21,28,55] and IL-17RA [31] in the gingival tissue of patients with periodontitis reported by other authors agree with the increase in RANKL reported by Bi CS et al. [54].

In addition to this, the positive correlation between IL-17A with PD and CAL in gingival tissue agrees with that reported by another study group [28]; the higher the IL-17A concentration, the greater the probing depth, and insertion loss. Therefore, IL-17A and IL-17RA positively correlate in the gingival tissue and appear to be crucial to the loss of insertion and alveolar resorption. This could be because when IL-17A binds to IL-17RA it triggers the expression of chemokines, pro-inflammatory cytokines, and metalloproteinases (MMPs), promoting a crucial pro-inflammatory environment for osteoclastogenesis and bone erosion in periodontitis [56].

When correlating the levels of IL-17A between the plasma samples and gingival tissues, an inverse behavior was observed. While in plasma, there is a decrease in IL-17A levels, in gingival tissue the levels of this cytokine increase. This is probably because plasma can only detect IL-17A released by cells. In contrast, in gingival tissue, it can determine whether IL-17A is bound to the receptor on the cell membrane or intracellularly.

Similarly, this is probably because that IL-17A in plasma is blocked by the sIL-17RA, as other authors have proposed [12]. This could explain the discrepancy of IL-17A levels in different biological fluids.

Furthermore to these findings, a positive correlation was found between IL-23 and IL-17A in the gingival tissue that coincides with the path of the IL-23/IL-17 axis since the production of IL-17A depends on the stimulus of IL-23 [6].

This study has some limitations, principally the effect size and power of IL-23R in plasma and IL-23 in gingival tissue that was inadequate to evaluate the complete behavior of the IL-23/IL-17 axis. Another limitation was the sample size; it is important to evaluate these molecules in more patients with periodontitis to have better study groups classified by the periodontal grades and stages, this can help to determine if there is a significant difference in the severity and progresion of periodontal disease.

In the future, the IL-23/IL-17A axis and their receptors in the gingival tissue of periodontitis patients will be analyzed by Western blot and mass spectrometry, which will allow us to study the functionality of the isoforms from the IL-23/IL-17 axis and their association with periodontitis progression in detail. In this sense, different biological drugs (monoclonal antibodies) have been used in different pathologies such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis to counteract the proinflammatory effect of various cytokines and receptors, including IL-17, IL-23, and IL-17RA, and extensive improvements have been observed in the clinical and histological features of these diseases [57–60]. For example, brodalumab, approved for the treatment of psoriasis, which consists of an IgG2a monoclonal antibody that specifically binds to IL-17RA and blocks the signaling of various IL-17 isoforms (IL-17A and IL-17F) [61,62]. It would be interesting to carry out the corresponding experimental phases to test this kind of brodalumab, because in this study, we found elevated IL-17RA in the gingival tissue of patients with periodontitis. In this way, it may be possible to reduce RANKL production by fibroblasts [9], and thus block bone resorption generated by the IL-17/IL-17RA and RANK/RANKL systems in patients with periodontitis.

5. Conclusions

The detection of the IL-23/IL-17 axis and its receptors in the gingival tissue provides more information on the behavior of the IL-23/IL-17 axis in a localized way, since it is found in the periodontal microenvironment, unlike the systemic evaluation as in plasma. In addition, elevated levels of IL-23, IL-17A, and IL-17RA were found in gingival tissues, and these findings correlate with clinical periodontal characteristics.

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