

# Local and Systemic Expression Profile of IL-10, IL-17, IL-27, IL-35, and IL-37 in Periodontal Diseases: A Cross-sectional Study

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## ABSTRACT

**Aim:** This study aimed to compare the level of interleukin (IL)-10, IL-17, IL-27, IL-35, and IL-37 in the gingival crevicular fluid (GCF) and human plasma of subjects with periodontal disease.

**Materials and methods:** In this cross-sectional study conducted over a 3-month period at a primary dental clinic in Malaysia, 45 participants were recruited via consecutive sampling and assigned into three groups, namely healthy periodontium group ( $n = 15$ ), gingivitis group ( $n = 15$ ), and periodontitis group ( $n = 15$ ). Gingival crevicular fluid and plasma samples were collected from each participant. Enzyme-linked immunosorbent assay test was conducted to measure the concentration of IL-10, IL-17, IL-27, IL-35, and IL-37. Kruskal–Wallis H test was used to compare the interleukin levels between patient groups.

**Results:** In GCF samples, IL-17 level was the highest in the periodontitis group ( $p < 0.05$ ), while IL-27 was the lowest ( $p < 0.05$ ). Meanwhile, plasma levels of IL-27 and IL-37 were significantly lower ( $p < 0.05$ ) in the periodontitis group, but plasma IL-35 levels were observed to rise with increasing disease severity.

**Conclusion:** There are reduced local and systemic levels of IL-27 in periodontitis patients.

**Clinical significance:** Periodontal diseases exert both local and systemic effects, resulting in the destruction of the tooth-supporting structures and contributing to the systemic inflammatory burden. Some of the cytokines that were investigated in the current study, IL-17, IL-27, IL-35, and IL-37, can be potential biomarkers that warrant further longitudinal clinical studies to determine their usefulness as prognostic/diagnostic markers.

**Keywords:** Cross-sectional study, Cytokine, Gingival crevicular fluid, Gingivitis, Interleukin, Periodontal disease, Periodontitis, plasma.

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## INTRODUCTION

Periodontal diseases are chronic inflammatory diseases affecting the tooth-supporting structures, namely gingiva, periodontal ligament, alveolar bone, and cementum. Up to 11% of the world's population was affected by variable degree of periodontal diseases.<sup>1</sup> Despite being initiated by the presence of bacterial biofilm, researches in the past few decades have unraveled the host's integral role in the pathogenesis and progression of periodontal diseases.<sup>2</sup> The interaction between host and pathogen is complex, involving many cells, antibodies, enzymes, and various biological molecules.

Cytokines are important modulators of the body's homeostasis and inflammatory processes. Their biological activities are diverse, but fundamentally, they act as initiator and regulator of the innate and adaptive immunity that underpin periodontal pathogenesis.<sup>3</sup> Moreover, cytokines mediate tissue loss that results in loss of function and clinical disease. It is proven that cytokines play a prominent role in osteoclast activation and the resultant bone resorption associated with periodontitis.<sup>4</sup> In simple terms, the balance between pro- and anti-inflammatory cytokines and modulation of their target receptors and signaling pathway dictate the degree of periodontal tissue destruction.<sup>3</sup>

Gingival crevicular fluid (GCF) is a physiological transudate as well as inflammatory exudate originated from the gingival plexus of blood vessels.<sup>5</sup> Cytokines are detected continuously in the gingival crevicular fluid (GCF). Their production is also upregulated in the

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systemic circulation due to the dissemination of oral bacterial endotoxin into the bloodstream.<sup>6</sup>

Extensive research effort had been directed toward investigating pro-inflammatory cytokines such as interleukin (IL)-1 $\beta$ , tumor necrosis factor- $\alpha$ , and IL-6.<sup>3</sup> Research into the roles of other cytokines in periodontal inflammation is ongoing. In particular, studies on inhibitory cytokines are required to facilitate the development of

cytokine-targeting therapies. These therapies work via blocking antibody, receptor antagonist, and anti-inflammatory cytokine.<sup>7</sup> Other than IL-10, which has an established suppressive effect on pro-inflammatory cell populations such as Th1 cells, Th2 cells, NK cells, and macrophages,<sup>8</sup> there is a gap in knowledge in relation to the roles of IL-27, IL-35, and IL-37 in periodontal etiopathogenesis. The available evidence in the literature suggested that they play an anti-inflammatory role.<sup>8–11</sup>

IL-17 meanwhile exhibits the properties of a pro-inflammatory cytokine. It can trigger osteoclastic activity causing bone resorption and inflammation in rheumatoid arthritis. Th17 cells, which secrete principally IL-17, have garnered much attention in periodontal research due to a recent discovery that they played a major role in the recruitment of neutrophils.<sup>12</sup> This is clinically significant because neutrophils play a substantial role in both tissue homeostasis and periodontal pathogenesis. Therefore, IL-17 is included along with the aforementioned anti-inflammatory cytokines in this study.

The objective of this study was to compare the levels of five different cytokines (IL-10, IL-17, IL-27, IL-35, and IL-37) in periodontal disease and health.

## MATERIALS AND METHODS

A cross-sectional study was conducted from January 2016 to March 2016 at Oral Health Centre (OHC), International Medical University (IMU), a university-based primary dental clinic located in an urban setting. Approval was obtained from IMU Joint Committee for Research and Ethics, approval number: BDS I1-13(01)2016 and BMSc I-1/2015(16).

Informed written consent was obtained from every participant. No ethical issues were encountered throughout the duration of the study. A flowchart of the study protocol is illustrated in [Flowchart 1](#).

### Sample Size Calculation

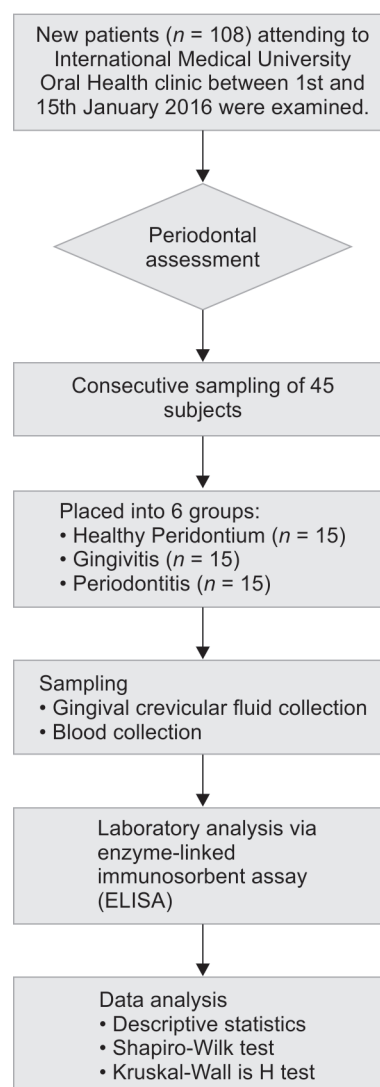
To achieve a confidence interval of 95% and power of 80%, we calculated our sample size to be 15 for each group, amounting to a total sample size of 45.

### Study Participant Selection

All new patients attending at OHC, IMU, from January 1 to January 15, 2016, and aged between 20 and 60 years old were screened by a single periodontally trained examiner. A total of 108 patients were examined. Out of the 108 patients, 45 patients satisfied the inclusion criteria and were approached to be study participants. The diagnosis and selection criteria were confirmed by a university lecturer specialized in the field of periodontics. Exclusion criteria include any systemic disease that can affect the periodontium (diabetes, pregnancy, and immunosuppression), smoking habit, periodontal treatment in the past 1 year, and any recent use of antibiotics or anti-inflammatory medications in the past 6 months.

The participants were selected based on clinical measurement of pocket depth (PD), clinical attachment loss (CAL), and bleeding on probing (BOP) score. The participants were then allocated into three groups: healthy periodontium (H), gingivitis (G), and periodontitis (P). The grouping criteria were as follows:

- Healthy periodontium (H): no site with CAL or PD > 2 mm, and BOP < 15%<sup>13</sup>
- Gingivitis (G): no site with CAL or PD > 2 mm, and BOP ≥ 20%<sup>13</sup>
- Periodontitis (P): at least two posterior sites in each of the upper quadrants with CAL and PD ≥ 5 mm, and BOP > 40%.<sup>14</sup>



Flowchart 1: Flowchart of the study protocol

A consent form was signed by all participants prior to the collection of samples. Samples were collected after breakfast between 9 a.m. and 11 a.m.

### Sample Collection

#### GCF Collection

For GCF collection, six sampling sites from the anterior maxillary or mandibular teeth were identified. In the periodontitis group, the six sites with the greatest probing pocket depth were identified. The anterior region was selected because it is easier for isolation with cotton roll to prevent salivary contamination. Six sterile paper points (ISO 30) were inserted gently into the gingival crevice and left in place for 60 seconds. Paper points that displayed blood contamination were discarded. The paper points were kept and sealed in sterile Eppendorf tubes and immediately stored in the laboratory refrigerator at –80°C.

#### Plasma Sample Collection

Two to three milliliters of venous blood was collected in an ethylenediaminetetraacetic acid (EDTA) Vacutainer. The blood

samples were centrifuged at 4°C for 15 minutes at 4000 rpm. The plasma samples were collected and kept in a 1.5 mL centrifuge tubes. The samples were stored at –80°C.

### Identification of the Cytokine Content

The levels of the interleukins were quantified using an enzyme-linked immunosorbent assay (ELISA) kit manufactured by Elabscience (USA). Standards and samples were prepared according to the manufacturer's guidelines. They were incubated for 90 minutes, at 37°C. Next, 100 µL of prepared biotin-detection working solution was added into all wells, and the plate was subsequently sealed, and samples were incubated for 60 minutes. Following that, 100 µL of prepared horseradish peroxidase–streptavidin conjugate working solution was added into all wells, and the samples were incubated for 30 minutes at 37°C. Then, 90 µL of tetramethylbenzidine substrate was added into each well, after which the plate was sealed, and samples were incubated for 20 minutes. The plate was read immediately at 450 nm after the addition of 50 µL STOP Solution into each well. A standard curve was plotted, and the concentration of the interleukins was extrapolated from the graph. The concentration of interleukins in GCF was multiplied by the dilution factor to account for dilution.

### Data Analysis

Statistical analysis was done using GraphPad prism 7.0. Shapiro–Wilk test was carried out to determine the normality of the data set. Subsequently, we used Kruskal–Wallis one-way analysis of variance to compare between three groups of quantitative variables with non-normal distribution and Fisher's exact test for comparison between categorical variables of gender and race. A *p* value of <0.05 was considered statistically significant.

## RESULTS

### Demographic Data and Clinical Parameters

There were more males (59.9%) and Chinese (64.5%) overall and within each individual group. The mean age for the healthy, gingivitis, and periodontitis groups was significantly different from one another at  $22.53 \pm 0.52$  years,  $30 \pm 12.76$  years, and  $55 \pm 13.36$  years, respectively ( $p < 0.05$ ) (Table 1). The periodontitis group exhibited significantly higher ( $p < 0.05$ ) probing depth,

plaque index, gingival index, and bleeding score when compared to the healthy and gingivitis groups (Table 1).

### Cytokine Levels in GCF

IL-17 levels in GCF of the periodontitis group were significantly higher ( $p < 0.05$ ) than the gingivitis group and healthy group (Fig. 1B). The lowest concentration of IL-27 was detected in the periodontitis group, with significant difference ( $p < 0.05$ ) when the periodontitis group was compared to either the healthy or gingivitis group ( $p < 0.05$ ) (Fig. 1C).

With regard to IL-10, IL-35, and IL-37, there was an increasing trend in cytokine levels as severity of periodontal disease increased, but no significant difference ( $p > 0.05$ ) was detected (Fig. 1A, 1D, and 1E).

### Cytokine Levels in Plasma

Plasma levels of IL-27 and IL-37 were significantly lower ( $p < 0.05$ ) in the periodontitis group compared to healthy and gingivitis groups (Fig. 2C and 2E). We observed the greatest concentration of IL-35 in the plasma of periodontitis patients, with significant difference when compared to patients with periodontal health or gingivitis ( $p < 0.05$ ) (Fig. 2D).

There was no significant difference ( $p > 0.05$ ) in the levels of IL-10 and IL-17 in the plasma, although the gingivitis group and periodontitis group were found with the highest levels of IL-10 and IL-17, respectively (Fig. 2A and 2B).

## DISCUSSION

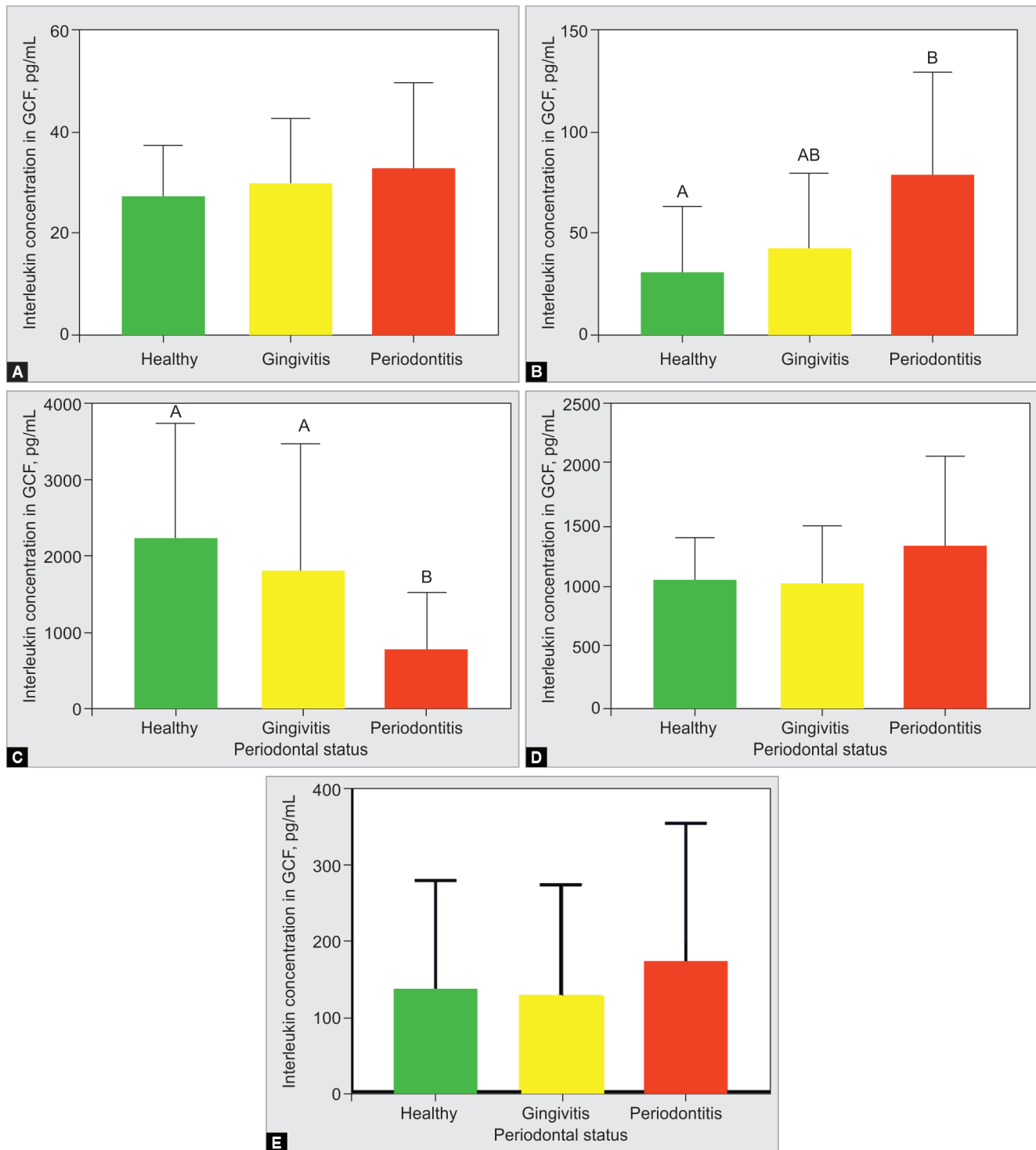
In this present study, a rising trend was observed for IL-17 levels in GCF and IL-35 levels in plasma. On the contrary, IL-27 levels in GCF and IL-27 and IL-37 levels in plasma followed a downward trend from healthy to periodontitis group.

IL-10 suppresses Th17 cell differentiation and promotes the production of immunoglobulins.<sup>15</sup> It has potent anti-inflammatory properties mediated by the heterodimeric IL-10 receptor. Receptor-ligand activation initiates a cascade of events that ultimately inhibits the release of pro-inflammatory mediators and reduces antigen presentation and phagocytosis.<sup>16</sup> In our study, IL-10 level in human plasma and GCF was not significantly different across groups. Other studies on periimplantitis, a condition with similar pathogenesis to periodontitis, also found no significant difference

**Table 1:** Demographics and clinical characteristics of healthy patients (H), gingivitis patients (G), and periodontitis patients (P)

	H (n = 15)	G (n = 15)	P (n = 15)	<i>p</i> value	Post hoc test <sup>c</sup>
Age, years (mean ± SD)	22.53 ± 0.52	30 ± 12.76	55 ± 13.36	<0.001 <sup>a</sup>	G/P*, H/P*
Gender					
Male (n, %)	9 (20.0)	8 (17.7)	10 (22.2)	>0.05 <sup>b</sup>	
Female (n, %)	6 (13.3)	7 (15.5)	5 (11.1)		
Race					
Malay (n, %)	6 (13.3)	4 (8.9)	1 (2.2)	<0.05 <sup>b</sup>	
Chinese (n, %)	8 (17.8)	7 (15.6)	14 (31.1)		
Indian (n, %)	1 (2.2)	1 (2.2)	0 (0)		
Others (n, %)	0 (0)	3 (6.7)	0 (0)		
Probing depth, mm (mean ± SD)	1.27 ± 0.21	1.79 ± 0.28	3.19 ± 0.51	<0.05 <sup>a</sup>	G/P*, H/P*
Gingival index (mean ± SD)	0.38 ± 0.27	1.31 ± 0.53	1.59 ± 0.65	<0.05 <sup>a</sup>	G/P*, H/P*
Plaque index (mean ± SD)	0.55 ± 0.34	1.25 ± 0.32	1.77 ± 0.57	<0.05 <sup>a</sup>	G/P*, H/P*
BOP% (mean ± SD)	7.02 ± 6.55	48.67 ± 15.44	68.39 ± 20.21	<0.05 <sup>a</sup>	G/P*, H/P*

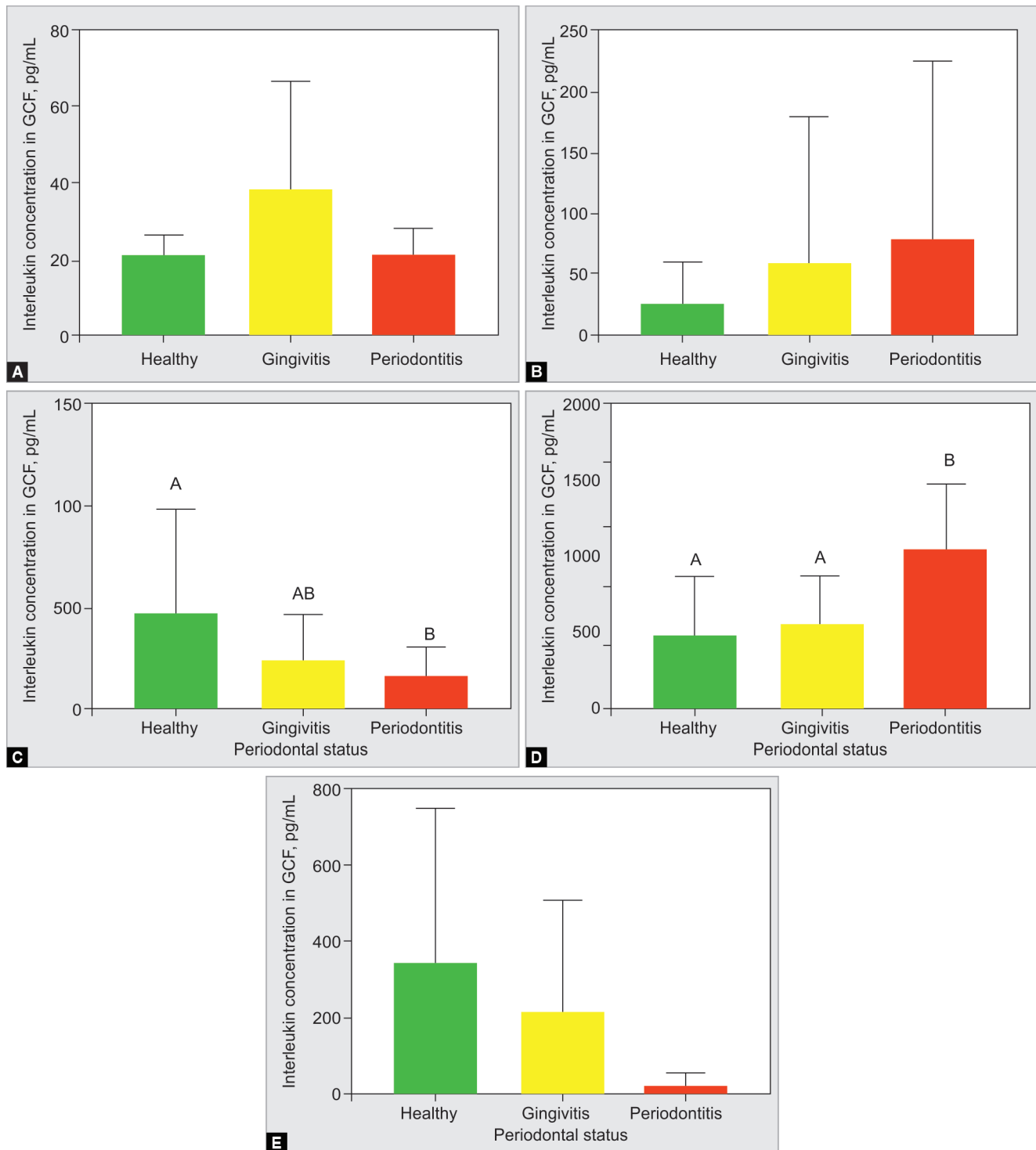
SD, standard deviation; BOP, bleeding on probing; asterisk (\*) denotes significant difference ( $p < 0.05$ ); <sup>a</sup>Kruskal–Wallis test; <sup>b</sup>Fisher's exact test; <sup>c</sup>Dunn's multiple comparison tests



**Fig. 1A to E:** Comparison in levels of (A) IL-10, (B) IL-17, (C) IL-27, (D) IL-35, and (E) IL-37 in gingival crevicular fluid (GCF) between healthy, gingivitis, and periodontitis groups. Means with different letters are significantly different (Kruskal–Wallis and Dunn's multiple comparison tests;  $p < 0.05$ ). Values are expressed in pg/mL

in IL-10 level within periimplant crevicular fluid and saliva with or without periimplantitis.<sup>17,18</sup> Additionally, tissue supernatants sampled from patients with chronic periodontitis were not characterized by excessive production of IL-10.<sup>19</sup> Interestingly, another study reported higher expression of IL-10 mRNA in gingival

biopsies of chronic periodontitis patients.<sup>20</sup> It was speculated that the higher expression of IL-10 accounted for the less severe form of the disease when compared to the rapidly progressing aggressive periodontitis, as IL-10 is associated with suppression of bone resorption.<sup>20</sup>



**Fig. 2:** Comparison in levels of (A) IL-10, (B) IL-17, (C) IL-27, (D) IL-35, and (E) IL-37 in plasma between healthy, gingivitis, and periodontitis groups. Means with different letters are significantly different (Kruskal–Wallis Test and Dunn’s multiple comparison tests;  $p < 0.05$ ). Values are expressed in pg/mL

Conversely, IL-17 is a pro-inflammatory cytokine produced by Th17 cell that serves the dual roles of protection and tissue destruction. On the protective side, IL-17 confers protective immunity against microbial pathogens by preserving barrier integrity, producing antimicrobial factors and granulocytes

such as neutrophils and macrophages.<sup>21</sup> Excessive production of IL-17, however, is associated with various immune-mediated inflammatory diseases including psoriasis, rheumatoid arthritis, and periodontitis.<sup>22</sup> IL-17 is capable of regulating destructive cytokines such as IL-6, IL-1, and IL-8. It can also promote the activation of



osteoclasts and potentiate neutrophilic inflammation, which might explain why IL-17 and the bone-resorbing factor RANKL were detected in abundance in alveolar bone of chronic periodontitis patients.<sup>18,21</sup> These properties could explain why in the present study, the highest level of IL-17 was detected in the periodontitis group for the GCF samples, with significant difference when compared to the healthy group. Inonu et al.<sup>23</sup> evaluated salivary IL-17 levels in different stages of periodontal disease and also found the greatest level in the periodontitis group.

IL-27 belongs to the IL-12/IL-23 heterodimeric family of cytokines with pleiotropic and opposing properties.<sup>9</sup> Healthy individuals were having the highest mean concentration of IL-27 in both GCF and plasma samples, followed by gingivitis group and periodontitis group. This result was in agreement with that of Han et al.,<sup>24</sup> who reported that individuals with periodontal health have higher level of IL-27 in GCF. Besides that, level of IL-27 in GCF raised upon completion of periodontal therapy.<sup>24</sup> With regard to plasma level of IL-27, a study in 2018 found out that the mean serum level increased after scaling and root planing procedures.<sup>25</sup> It can be speculated that the presence of IL-27 subdues the inflammatory responses via suppression of Th1 and Th2 responses. Moreover, IL-27 could induce Foxp3-IL-10-producing cells to produce IL-10, which helps to control inflammation as well as lowering the secretion of other pro-inflammatory cytokines.<sup>9</sup>

As part of the IL-12 cytokine family, IL-35 is known as an anti-inflammatory cytokine involved in the generation of regulatory T ( $T_{reg}$ ) cells, which suppress the proliferation of effector T cells.<sup>10</sup> However, a clinical study on the association between IL-35 and periodontal disease demonstrated that IL-35 total amount was significantly higher in the periodontitis group.<sup>26</sup> EB13 and IL12AmRNA, two components of the IL-35 protein, were expressed at a significantly higher level in the gingival tissue samples of periodontitis patients.<sup>27</sup> The present study, however, discovered no significant difference among groups, despite demonstrating an increasing trend as periodontal disease progressed. Periodontal disease is characterized by periods of quiescence and active destruction.<sup>28</sup> Since IL-35 might be overexpressed during period of active destruction to prevent excessive host damage to the periodontium, the lack of difference in the present study might be attributed to the dormancy stage of the periodontal disease sites sampled. It is also possible that the sample size was too small to detect a significant difference. With regard to plasma levels of IL-35, we found a steady increase from healthy group to periodontitis group. This was in contrast to previous studies, which concluded that periodontal diseases do not affect the plasma level of IL-35.<sup>26,29</sup> Despite no significant difference, the plasma level of IL-35 in Raj et al.<sup>29</sup> study was highest in the periodontitis group, and the mean plasma concentration was higher following nonsurgical periodontal therapy. A recent study corroborated our study findings by reporting that subjects with chronic periodontitis had significantly higher mean concentration of IL-35 ( $p < 0.001$ ) compared to healthy subjects.<sup>30</sup> Hence, we speculated that IL-35 plays a part in maintaining the homeostasis of the local microenvironment and thus limiting the progression of chronic periodontitis.

A study by Saglam and colleagues<sup>31</sup> on the association between IL-37 level and periodontal disease found out that IL-37 concentration was significantly lower in the GCF of the periodontitis group, but no difference was noted among the human plasma samples. This was in contrast to our results, which found significantly lower concentration of IL-37 in human plasma, but not GCF samples. As a member of the IL-1 family, IL-37 is an inhibitory cytokine that plays a regulatory role in both innate and adaptive

immunity.<sup>32</sup> Recent in vitro studies indicated that IL-37 could exert a dose-dependent inhibitory effect on osteoclast formation.<sup>33</sup> IL-37 is involved in chronic inflammatory conditions and has shown uniqueness in being upregulated by pro-inflammatory cytokines while being able to inhibit the secretion of IL-1 $\beta$ -induced pro-inflammatory cytokines.<sup>34</sup> This contrasting behavior could explain the absence of any difference in the GCF levels among our study participants, while the local periodontal inflammation had an effect on the systemic levels of IL-37. A consistent feature was the reduced concentration of IL-37, an inhibitory cytokine when periodontal disease was in the advanced stage.

The limitation of this study was the small sample size that had resulted in data that followed a non-normal distribution. Moreover, there were significant age and ethnicity differences between the patient groups, which could be potential confounders. The nonprobability sampling method used in this study might introduce selection bias, because patients who attended to the dental clinic might have better oral health status than the nonattendees. Therefore, the results are not generalizable. The activity and progression of periodontal diseases depend on the balance between pro- and anti-inflammatory mediators. Therefore, future studies should employ a bigger sample size, evaluate the change in cytokine levels associated with periodontal disease on a longitudinal basis, and investigate the ratio of pro- against anti-inflammatory cytokines, which could yield more meaningful results and decipher the role of these cytokines in the initiation, development, and progression of periodontal disease.

## CONCLUSION

Within the limitation of our study, we arrived at a conclusion that levels of IL-17 and IL-27 in GCF can vary depending on the severity of periodontal disease. Moreover, local inflammation of the periodontium leads to detectable differences in the systemic levels of IL-27, IL-35, and IL-37. These cytokines should be the targets of further multicenter, longitudinal studies in order to elucidate the exact role of these proteins in the pathogenesis of periodontal diseases and explore the possibility of using them as biomarkers and prognostic markers that can allow us to predict an individual's susceptibility to the development and progression of periodontal diseases.

## CLINICAL SIGNIFICANCE

Periodontal diseases exert both local and systemic effects, resulting in the destruction of the tooth-supporting structures and contributing to the systemic inflammatory burden. Some of the cytokines that were investigated in the current study, IL-17, IL-27, IL-35, and IL-37, can be potential local or systemic biomarkers that warrant further longitudinal clinical studies to determine their usefulness as prognostic/diagnostic markers.

## ACKNOWLEDGMENTS

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**Ethical Policy and Institutional Review Board Statement:** Ethical approval was obtained from the International Medical University (IMU) Research Joint Committee with approval number BDS I1-13(01)2016 and BMSc I-1/2015(16). All the procedures have been conducted in accordance with the ethical guidelines laid down by the Declaration of Helsinki (2013).

**Patient Declaration of Consent Statement:** Information sheet and written consent form were presented to participants prior to commencement of the study. Informed consent was obtained from all subjects who agreed to be a part of this research.

**Data Availability Statement:** The data set used in the current study is available on request from Dr. Pulikkotil Shaju Jacob at shaju\_jacob@imu.edu.my.

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