Estimation of YKL-40 Acute-Phase Protein in Serum of Patients with Periodontal Disease and Healthy Individuals: A Clinical-Biochemical Study

Abstract

Objective: YKL-40, an acute-phase protein, is a novel potential inflammatory marker. It is a member of “mammalian chitinase-like proteins.” YKL-40 is secreted by activated neutrophils and macrophages in both acute and chronic inflammation. It is also shown to be produced by vascular smooth muscle and endothelial cells, arthritic chondrocytes, cancer cells, and embryonic and fetal cells. It might play an important role in the initiation or maintenance of pro-inflammatory response. The purpose of the present study was to estimate the concentrations of YKL-40 in the serum of healthy and periodontally affected individuals. Materials and Methods: Serum samples were collected from forty patients of periodontally (Group C) affected sites (probing depth [PD] ≥5 mm) and gingivitis patients (Group B) affected sites (PD ≤ 3 mm) with bleeding on probing. Comparison with healthy controls was carried out by collecting serum samples from ten healthy volunteers (Group A). 5 ml of blood was collected from the antecubital fossa by venipuncture using a 20G needle with 5 ml syringe and immediately transferred to the laboratory. Serum was extracted from blood and stored at −70°C till the assay procedure, and enzyme-linked immunosorbent assay was performed to determine the concentrations of YKL-40. Results: The mean YKL-40 concentration scores were significantly higher in Group C, i.e. 62.49 ± 8.33 when compared to Group B, i.e. 51.96 ± 4.30 and Group I, i.e. 44.23 ± 4.34, which was statistically significant (P ≤ 0.001). In the present study, mean probing pocket depth was higher in Group C than Group A (P ≤ 0.001). A positive correlation was found between probing pocket depth and concentrations of YKL-40 in serum (r = 0.815), P < 0.001, i.e. when the pocket depth increases, concentration of YKL-40 also increases. Conclusion: In this study the presence of YKL-40 in serum samples was observed both in healthy and chronic periodontitis. In this study, the concentration of YKL-40 was elevated in chronic periodontitis group when compared to healthy group. With increases in the amount of destruction, there is substantial increase in clinical parameter and YKL-40 concentration in serum, which is directly related to pocket depth. This study shows that YKL-40 is a novel biomarker for periodontal disease progression.

Keywords: Periodontitis, probing pocket depth, YKL-40

Introduction

Periodontitis is a chronic inflammatory disease initiated by microbial infections that lead to a host response resulting in inflammatory breakdown of tooth- supporting osseous and soft tissues.[1] The presence of periodontopathogens, primary etiologic agents for disease initiation, is necessary but is inadequate for the progression and severity of disease. The onset, progression, and severity of periodontal disease are related to the interaction between periodontal microorganisms and the host immune response.[1] In response to bacterial endotoxins, the mediators such as acute-phase proteins (APP), cytokines, and prostaglandins are produced as a part of host response, which may cause tissue destruction.[2,3] APPs are defined as proteins whose serum concentration is altered at least 25% in response to inflammation. The acute-phase response (APR) is a prominent systemic reaction of the host to local or systemic disturbances in its homeostasis caused by infection, tissue injury, trauma or surgery, or immunological disorders. It occurs approximately 90 min after the onset of inflammatory reaction. The purpose of these responses is to restore homeostasis and to remove the cause of the disturbance.[4] APPs are a class of proteins whose plasma concentration increases or decreases in

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response to inflammation. APPs are the sensitive markers for evaluating the status of inflammation. Increased levels of APP are associated with increased risk for cardiovascular events in both health and coronary heart disease patients and have been suggested to associate with infectious disease such as periodontitis.[4]

The Gram negative organisms in sub gingival plaque samples of periodontitis releases endotoxins which will interact with toll-like receptors (TLR) that are expressed on the surface of polymorphonuclear leukocytes (PMNs) and monocytes which are in more at the inflammatory site. The complex formed due to interaction of endotoxins and TLR activates the signal transduction pathway in both innate and adaptive immunities, resulting in the production of cytokines and C-reactive protein and fibrinogen[5,6] that co-ordinate the local and systemic inflammatory responses. As a part of nonspecific response, pro-inflammatory cytokines originating at the diseased site activate the liver cells to produce APPs.[4]

The APP is also stimulated by the release of cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha from macrophages and monocytes at the site of inflammatory lesions or infections.[7]

There is evidence that acute-phase cytokines and acute-phase reactants are released and associated with tissue breakdown in periodontal disease.[1]

YKL-40, an APP, is a novel potential inflammatory marker. It is a member of “mammalian chitinase-like proteins.”[8] YKL-40 is secreted by activated neutrophils and macrophages in both acute and chronic inflammation.[9] It is also shown to be produced by vascular smooth muscle endothelial cells, arthritic chondrocytes, cancer cells, and embryonic cells.

Data show that levels of various APPs increased in periodontal disease in both gingival crevicular fluid (GCF) and plasma or serum.[2,4] Therefore, they can be used as a susceptible marker in relation to inflammatory status.[1] Human cartilage glycoprotein 39 (HCgp39) is also known as chitin-binding glycoprotein. The abbreviation YKL-40 is based on the first three N-terminal amino acids, tyrosine (Y), lysine (K), and leucine (L) and the molecular weight of YKL-40. The CHI3L1 gene for human YKL-40 highly conserved area on chromosome 1q31-q32. YKL-40 belongs to the family 18 of glycosyl hydrolases comprising chitinases from various species.[10]

Although the exact functions of YKL-40 are still unknown, it probably has a role in cell proliferation, adhesion, migration, differentiation, inflammation, and protection from apoptosis. It is important to note that YKL-40 is highly multifunctional and could play a central role primarily in pathologic conditions associated with the homeostasis of connective tissue.[4]

YKL-40 APP can be used for the assessment of general health. APPs are more useful for monitoring periodontal health than cytokines since cytokines are cleared from the circulation within a few hours, whereas APP levels after a single stimulus remain unchanged for 48 h or longer.[3]

YKL-40, a new APP, is shown to be elevated in inflammatory diseases, such as rheumatoid arthritis,[11] type 2 diabetes mellitus,[12] coronary artery diseases,[13] and acute myocardial infarction.[14]

Materials and Methods

Following complete medical and dental examination, forty individuals were selected for the study from the Department of Periodontics, Meghna Institute of Dental Sciences, Mallaram (village), Nizamabad. This project was reviewed by the Board of Ethical Committee at Meghna Institute of Dental Sciences, and the project was envisaged after the clearance was obtained. A total of forty systemically healthy individuals were divided into three groups: Group A, healthy individuals; Group B, gingivitis patients; and Group C, chronic periodontic patients. Informed consent was obtained from each individual.

Inclusion criteria

Individuals were placed into three groups according to the following definitions:

- Group A (healthy controls; n = 10) comprised clinically healthy gingiva (Gingival Index [GI] = 0) and probing depth (PD) ≤3 mm without any clinical attachment loss (AL) or bone loss
- Group B (gingivitis group; n = 15) included patients with clinical findings, such as red color, swelling, GI ≥2, PD ≤3 mm with bleeding on probing (BOP), and no AL or radiographic bone loss
- Group C (chronic periodontitis group; n = 15) had GI ≥2, PD ≥5 mm with BOP, clinical attachment level (CAL) ≥2 mm, and radiographic bone loss.

Exclusion criteria

Current smokers, pregnant and lactating women, individuals with systemic disorders, patients under any medication for the past 6 months, and patients who had undergone any dental treatment for the past 6 months were excluded from the study.

Periodontal assessment

Periodontal disease status was evaluated at four sites per tooth (mesiobuccal, buccal, distobuccal, and lingual/palatal) by measuring the PD, CAL, Russel’s Index by A. L. Russell, GI by Loe and Silness, and plaque index (Silness and Loe) using the same periodontal probe (UNC-15 probes, Hu-Friedy, USA) and by the same examiner to avoid bias. The PD was measured as the distance from the gingival margin to the base of the pocket in millimeters. The CALs were calculated from the recession and PD measures and represented as the distance in millimeters from the cementoenamel junction to the base of the pocket.
Sample collection

Venous blood was withdrawn from the participants selected for the study. The participants were informed and consent was taken. They were made to tighten a fist so that vein was more palpable, and the antecubital vein was selected for venipuncture. A tourniquet was applied about 1–2” above the antecubital fossa. After cleansing the puncture site with 10% isopropanol solution, blood was withdrawn using a syringe with 24G needle. Tourniquet was released as the blood flow began. After drawing 5 mL of blood, sterile cotton ball was placed on the puncture site and needle was withdrawn. The participants were instructed to apply mild finger pressure on the site for few minutes to avoid oozing out of blood.

Human cartilage glycoprotein 39 (YKL-40) determination

Samples were centrifuged in the centrifuge machine at 1000 rpm for 15 min to separate the serum from blood. The separated serum was collected in Eppendorf tube and stored in deep freeze at −70°C. Quantitative determination of YKL-40 in patient’s serum was done by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) method.

Principle of the assay

Quantitative determination of YKL-40 in patient’s serum was done by double-antibody sandwich ELISA method. In this assay, the YKL-40 present in sample reacts with anti-YKL-40 antibodies, which had been adsorbed to the surface of polystyrene microtiter wells. After the removal of unbound sample proteins by washing, anti-YKL-40 antibodies conjugated with horseradish peroxidase were added. These enzyme-labeled antibodies form complexes with the previously bound sample YKL-40. The enzyme bound to the immunosorbent was assayed by addition of 100 µl of chromogenic substrate solution to each well. The wells were incubated for 10 min at room temperature and then protected from light following washing step. The quantity of bound enzyme varies directly with the concentration of YKL-40 in the test sample.

The quantity of YKL-40 in the test sample can be interpreted from the standard curve obtained from optical density values.

Statistical analysis

Data were presented as mean, standard deviation (SD), and 95% confidence interval of the mean difference. Comparison of three groups (healthy, gingivitis, and periodontitis) with respect to YKL-40 values was done using one-way analysis of variance.

Correlation between variables was found by Pearson’s correlation coefficient “r,” and all levels of significance were set at $P < 0.05$.

Results

Table 1 shows demographic characteristics of the study population. There was no statistically significant difference present in the mean age when the various groups were compared ($P \geq 0.05$) [Table 1].

Table 2 shows the mean values of various clinical parameters in the study groups. There was statistically significant difference in the mean values among various groups ($P \leq 0.001$). However, the mean difference was higher in Group C compared to Group B and Group A [Table 2].

The mean YKL-40 concentration scores were 44.23, 51.96, and 62.49 ng/ml in Groups A, B, and C, with SD of 4.34, 4.30, and 8.33, respectively. The mean YKL-40 concentration scores were compared, which were significantly higher in Group C, i.e., 62.49 ± 8.33 when compared to Group B, i.e. 51.96 ± 4.30 and Group A, i.e. 44.23 ± 4.34, which was statistically significant, $P \leq 0.01$ [Table 3].

A positive correlation was found between YKL-40 concentration and correlation coefficient values of the various clinical parameters. There was statistically significantly high positive correlation present between the YKL 40 values and various clinical parameters such as plaque index ($r = 0.783$), GI ($r = 0.674$), probing pocket depth ($r = 0.815$), CAL ($r = 0.832$), and Russel’s periodontal index ($r = 0.784$) [Table 4].

The mean concentration on YKL-40 from site with probing pocket depth of 5 mm, 6 mm, 7 mm, 8 mm, and

| Table 1: Age and sex distribution of the study population |
| --- |
| Gender | Group A | Group B | Group C | $P$ |
| **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** |
| Female | 5 | 37.20±2.86 | 8 | 37.85±1.45 | 7 | 39.24±4.24 | 0.079 (NS) |
| Male | 5 | 35.80±4.32 | 7 | 36.14±3.62 | 8 | 38.15±5.39 | 0.057 (NS) |
| Total | 10 | 36.50±3.53 | 15 | 37.06±2.73 | 15 | 38.44±5.16 | 0.218 (NS) |
| **NS:** Not significant ($P>0.05$). SD: Standard deviation |

| Table 2: Comparison of clinical parameters in various groups (one-way ANOVA) |
| --- |
| Clinical parameters | Group A | Group B | Group C | $P$ |
| Plaque index | 0.39±0.07 | 1.47±0.14 | 2.65±0.20 | <0.001** |
| Gingival index | 0.27±0.07 | 2.63±0.29 | 2.90±0.08 | <0.001** |
| Probing pocket depth | 1.50±0.53 | 2.33±0.49 | 6.67±1.35 | <0.001** |
| Clinical attachment level | 0.00±0.00 | 0.00±0.00 | 7.07±2.31 | <0.001** |
| Russel’s index | 0.14±0.03 | 0.85±0.07 | 4.33±0.40 | <0.001** |
| **Highly significant ($P<0.01$). SD: Standard deviation** |
10 mm was 62.20 ng/ml, 59.28 ng/ml, 58.17 ng/ml, 73.00 ng/ml, and 81.50 ng/ml respectively. Serum concentration of YKL-40 was increased with increased in probing depth which was statistically significant ($P = 0.005$) [Table 5].

The serum concentrations of YKL-40 were compared between probing pocket depth of 6 mm and 7 mm. The mean concentration of YKL-40 was lesser in probing pocket depth of 7 mm, i.e. 58.175 ng/ml than from the site with probing pocket depth of 6 mm, i.e. 59.28 ng/ml, which was statistically not significant with a mean difference of 1.1 ($P = 0.714$).

The serum concentrations of YKL-40 were compared between probing pocket depth of 7 mm and 8 mm. The mean concentration of YKL-40 was higher in probing pocket depth of 8 mm, i.e. 73.00 ng/ml than from the site with probing pocket depth of 7 mm, i.e. 58.1 ng/ml, which was statistically significant with a mean difference of −14.8 ($P \leq 0.001$).

The serum concentrations of YKL-40 were compared between probing pocket depth of 6 mm and 8 mm. The mean concentration of YKL-40 was higher in probing pocket depth of 8 mm, i.e. 73.00 ng/ml than from the site with probing pocket depth of 6 mm, i.e. 59.28 ng/ml, which was statistically significant with a mean difference of −13.7 ($P \leq 0.001$) [Table 6].

### Table 3: Intergroup comparison of biochemical parameter

| Biochemical parameter | Mean±SD | $P$   |
|-----------------------|--------|-------|
| **Concentration of YKL-40**| 44.23±4.34 | 51.96±4.30 | 62.49±8.33 | <0.001** |

**Highly significant ($P<0.01$). SD: Standard deviation

### Table 4: Correlation of various clinical parameters with biochemical parameter (YKL 40)

| Parameter | Statistics | Age | PI | GI | PPD | CAL | RI | Concentration YKL-40 |
|-----------|------------|-----|----|----|-----|-----|----|-------------------|
| Concentration of YKL-40 | Pearson’s correlation coefficient ($r$) | 0.276 | 0.783** | 0.674** | 0.815** | 0.832** | 0.784** | 1 |
| | Significant (two tailed) | 0.085 (NS) | <0.001** | <0.001** | <0.001** | <0.001** | <0.001** | 1 |
| | $n$ | 40 | 40 | 40 | 40 | 40 | 40 |

NS: Not significant ($P>0.05$); **Highly significant ($P<0.01$). PI: Plaque index; GI: Gingival index; PPD: Periodontal pocket depth; CAL: Clinical attachment level; RI: Russell’s index

### Table 5: Comparison of concentrations of YKL40 at various levels of periodontal probing depths in periodontitis group

| Periodontal probing depth | Number of subjects | Minimum | Maximum | Mean | SD | $P$   |
|---------------------------|--------------------|---------|---------|------|----|-------|
| 5.0                       | 1                  | 62.2    | 62.2    | 62.200 | -  | 0.005** |
| 6.0                       | 7                  | 53.4    | 65.7    | 59.286 | 4.2393 |
| 7.0                       | 4                  | 53.5    | 67.6    | 58.175 | 6.5820 |
| 8.0                       | 2                  | 71.6    | 74.4    | 73.000 | 1.9799 |
| 10.0                      | 1                  | 81.5    | 81.5    | 81.500 | -  | 0.005** |

**Highly significant ($P<0.01$). SD: Standard deviation

### Discussion

Periodontitis is a disease of the periodontium characterized by loss of connective tissue attachment and supporting alveolar bone. These changes often lead to an esthetically and functionally compromised dentition. The pathogenesis of periodontal disease is an inflammatory process involving innate and adaptive immune responses.\(^{[15]}\)

Periodontopathogens are primary etiologic agents for disease initiation, but they are inadequate for the progression and severity of disease. The onset, progression, and severity of periodontal disease are related to the interaction between periodontal microorganisms and the host immune response.\(^{[1]}\)

Infection, tissue injury, trauma or surgery, or immunological disorders cause the APR which is characterized as a prominent systemic reaction of the host to local or systemic disturbances in its homeostasis. It is critical to the body’s ability to successfully respond to injury. It normally lasts only few days; however, if continuously unchecked, the APR may contribute to the development of chronic inflammatory states, tissue damage, and disease.\(^{[10]}\)

APPs are the sensitive markers for evaluating the status of inflammation. The rise in the plasma concentration of APPs assists host defense by aiding in the recognition of invading microbes, mobilization of leukocytes into the circulation, and increasing blood flow to injured or infected sites. Increased levels of APP are associated with increased risk for cardiovascular events in both healthy and coronary heart disease patients and have been suggested to associate with infectious disease such as periodontitis.\(^{[17,18]}\)

In the pathogenesis of periodontitis, PMNs and monocytes which are in abundance at the inflammatory site express
Table 6: Mean difference in YKL-40 values on comparison of various probing depths

| Periodontal probing depth | Mean difference | P       |
|--------------------------|----------------|---------|
| 6 versus 7               | 1.1            | 0.714 (NS) |
| 7 versus 8               | −14.8          | <0.001** |
| 6 versus 8               | −13.7          | <0.001** |

NS: Not significant (P>0.05), **Highly significant (P<0.01).

TLRs on their surface which interact with the endotoxins released from Gram-negative organisms present in the subgingival plaque samples. Cytokines, C-reactive protein, and fibrinogen are produced due to the complex formed due to the interaction of endotoxins, and TLR activates the signal transduction pathway in both innate and adaptive immunities. The pro-inflammatory cytokines originating at the diseased site activate the liver cells to produce APPs as a part of nonspecific response.

APPs are more useful than cytokines for monitoring periodontal health, since the latter are cleared from the circulation within a few hours, whereas APP levels after a single stimulus remain unchanged for 48 h or longer.

Data show that levels of various APPs increased in periodontal disease in both GCF and plasma or serum. Therefore, they can be used as a susceptible marker in relation to inflammatory status.

YKL-40, an APP, is a novel potential inflammatory marker. It is a member of “mammalian chitinase-like proteins.” HCgp39 is also known as chitin-binding glycoprotein. The abbreviation YKL-40 is based on the first three N-terminal amino acids, tyrosine (Y), lysine (K), and leucine (L) and the molecular weight of YKL-40. The CHI3L1 gene for human YKL-40 highly conserved area on chromosome 1q31-q32. YKL-40 belongs to the family 18 of glycosyl hydrolases, comprising chitinases from various species.

YKL-40 also modulates vascular endothelial cell morphology by promoting the formation of branching tubules, indicating that YKL-40 has a role in angiogenesis by stimulating the migration and reorganization of vascular smooth muscle cells.

Studies suggest a role of YKL-40 in the differentiation of monocytes to lipid-laden macrophages during formation of the atherosclerotic plaque.

It is well known that the pathogenesis of rheumatoid arthritis and periodontitis is substantially similar. Growing clinical evidence reveals that increased expression and secretion of YKL-40 contributes to the pathogenesis of rheumatoid arthritis. Moreover, YKL-40 is believed to be an independent indicator of disease activity in patients with rheumatoid arthritis.

Data suggest that acute-phase reactants might be related to the inflammatory status of periodontal tissues and that YKL-40 is released by a variety of cells, mainly neutrophils and macrophages that are significantly excessive during periodontal inflammation.

YKL-40, a new APP, is shown to be elevated in inflammatory diseases, such as rheumatoid arthritis, type 2 diabetes mellitus, coronary artery diseases, and acute myocardial infarction.

YKL-40 (CHI3L1) is secreted by a variety of cell types, including neutrophils, macrophages, and endothelial cells, and its mRNA is expressed in osteoblasts and osteocytes. Lipopolysaccharide induces the expression of YKL-40 (HC-gp39) mRNA in human monocytes; YKL-40 expression increases during the differentiation of osteoclasts from monocytes and it represents decreased bone resorption activity. In contrast, human gingival keratinocytes and fibroblasts and oral keratinocytes hardly express the CHI3L1 gene by DNA microarray analysis. The study shows that YKL-40 in GCF may be derived from neutrophils, macrophages, endothelial cells, osteoclasts, and osteocytes in periodontal tissues.

The present study investigating the serum concentration of YKL-40 in periodontal diseases showed that the total amount of serum YKL-40 levels clearly increased in patients with periodontitis compared with healthy individuals. Moreover, serum YKL-40 levels were higher in the chronic periodontitis group than in the gingivitis group. There is an increased serum YKL-40 level in several diseases characterized by inflammation.

In the present study, the mean concentrations of YKL-40 in serum were found to increase progressively from healthy (44.23 ng/ml) to periodontitis sites (62.49 ng/ml). This result of the study is in accordance with that of Keles et al. who also reported raised YKL-40 concentration in serum of periodontitis site.

In the present study, serum YKL-40 concentration correlated with the clinical parameters. Concentration of YKL-40 showed a positive correlation with the clinical parameters ($r = 0.783, P < 0.001$; $r = 0.674, P < 0.001$; $r = 0.815, P < 0.001$; $r = 0.832, P < 0.001$; and $r = 0.784, P < 0.001$, i.e. when clinical parameter scores increase, concentrations of YKL-40 also increase. This result of the study is in accordance with that of Kido et al. who also reported raised YKL-40 concentration in GCF in periodontitis site.

From the analysis of the relationship between YKL-40 concentration and probing pocket depth, it was found that there was a high correlation between the concentration of YKL-40 and probing pocket depth ($r = 0.832, P < 0.001$), i.e. when the pocket depth increases, concentrations of YKL-40 also increase, and there was a significant statistical difference between 7 mm and 8 mm pocket depth with a mean difference of $-14.11$, $P < 0.001$, and 6 mm and 8 mm pocket depth with a mean difference of $-14.8$, $P < 0.001$.
pocket depth with a mean difference of −13.7, P < 0.001. Thus, change in the concentration of YKL-40 remains a good indicator of periodontal disease progression. This result of the study is in accordance with that of Kido et al.[27] who also reported that the amount of YKL-40 in GCF was highly correlated with PD of GCF-collecting sites (P < 0.01), and its concentration was also significantly correlated with PD (P < 0.01).

In the present study, YKL-40 levels are examined in the presence of gingival inflammation (in gingivitis) and periodontal tissue breakdown (in chronic periodontitis), which allowed for the examination of the levels of YKL-40 molecule in different stages of periodontal disease. It has been shown that YKL-40 levels increase with age.[1,20] Therefore, age differences may influence the results of the study which were prevented by selecting individuals within a specific age group. Accordingly, study groups had similar ages in the present study. Although studies reported no effect of sex on serum or plasma YKL-40 levels,[1,20] the possible effect of sex on YKL-40 was minimized by including an equal number of males and females in the present study.

The present study clearly shows that the total amount of YKL-40 in serum is higher in patients with periodontal tissue breakdown. YKL-40 levels gradually increased from healthy to gingivitis groups and gingivitis to chronic periodontitis groups, and YKL-40 is considered to be associated with the severity of periodontitis.

Limitations of the present study

1. Larger sample sizes are required to get significant results
2. Long-term clinical trials are required to assess the effect of periodontitis on YKL-40 APPs
3. Single-point evaluation of YKL-40 levels may not reflect its long-term average.

Conclusion

The present study clearly shows that a total amount of YKL-40 in serum is higher in patients with periodontal tissue breakdown.

YKL-40 concentrations gradually increased from healthy to gingivitis group and gingivitis to chronic periodontitis group, and YKL-40 is considered to be associated with the severity of periodontitis.

However, further long-term studies upon larger sample size are required to quantitatively assess the relationship between YKL-40 APP and severity of periodontitis.

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Conflicts of interest

There are no conflicts of interest.

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