ORIGINAL RESEARCH

Salivary Fructosamine and Its Association with Interleukin-6 in Prediabetic Patients with and without Chronic Periodontitis: A Cross-sectional Study

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Abstract

Aim: The present study aimed to evaluate the association between prediabetes with chronic periodontitis utilizing glycated proteins like fructosamine and inflammatory markers like interleukin-6 (IL-6).

Materials and methods: This cross-sectional study was conducted on 36 subjects for a duration of approximately 7 months (between August 2021 and February 2022) screened for random blood sugar (RBS) levels (110–170 mg/ dL) and glycated hemoglobin (HbA1C) levels (5.7–6.4%) as prediabetes and were grouped into three groups ($n = 12$)—group I—systemically healthy with chronic periodontitis; group II—prediabetic with chronic periodontitis; group III—prediabetic without chronic periodontitis. The periodontal health was evaluated by employing bleeding on probing (BOP), clinical attachment loss, Loe and Silness Gingival Index, and pocket depth. Unstimulated whole saliva (UWS) samples were obtained and subjected to enzyme-linked immunosorbent assay (ELISA) for the evaluation of fructosamine and IL-6 levels. Data were analyzed by Statistical Package for the Social Sciences (SPSS) version 2.0.

Results: The intragroup comparison of salivary IL-6 values were highest among group II (52 ± 73) followed by group I (47 ± 71.7), and then group III (17.8 ± 17.8), while the intragroup comparison of salivary fructosamine values were highest among group I (2.4 ± 1.1) followed by group II (2.0 ± 1.1), and then group III (1.7 ± 0.8) which were statistically highly significant. ($p < 0.001$). Intergroup comparison revealed no significant difference between salivary IL-6 and fructosamine levels. Although mean fructosamine levels tended to be slightly lower in prediabetic individuals without periodontitis, it was not statistically significant.

Conclusion: Considering the alarming prevalence of undiagnosed diabetes around the world and the benefits of early illness detection, it's obvious to notice why diabetes screening with noninvasive markers like salivary fructosamine is so significant.

Clinical significance: Periodontitis may be associated with prediabetes, which is categorized by impaired glucose tolerance. Early detection of diabetes utilizing noninvasive indicators, such as salivary fructosamine, which appears to become more stable with time due to improved stability against microbiological deterioration, may help to reduce the tissue damage caused by the disease. The present study verifies the dentist's involvement and highlights the importance of focusing on chronic periodontitis patients in this situation.

Keywords: Fructosamine, Hyperglycemia, Inflammation, Interleukin-6, Periodontitis, Prediabetes, Saliva.

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Introduction

As the worldwide epidemic of type 2 diabetes worsens, it is worth reconsidering our strategy to prediabetes. A lot of progress has been made recently in regard to prediabetes screening, diagnosis, pathophysiology, and clinical intervention that enables reversing the diabetes pandemic likely. The phrase "prediabetes" refers to a group of dysglycemic conditions that lie anywhere between normal glucose regulation (NGR) and diabetes.[1] Although not everyone with prediabetes will develop diabetes, the majority of individuals with prediabetes may develop diabetes at some point in their lives.[2] Nevertheless, even when overt diabetes is averted or delayed, prediabetes patients tend to have a higher risk of micro and macrovascular complications than their normoglycemic counterparts. As a result, there is an emerging consensus that NGR ought to be the focus for prediabetics.[3]

When compared to systemically healthy individuals, chronic periodontitis is a widespread illustration in subjects with prediabetes (poor glucose tolerance).[4] It's plausible that persistent hyperglycemia in prediabetic patients induces an imbalance between host immune response and periodontal pathogens, leading to upregulation of proinflammatory cytokines, dysfunction of polymorphonuclear leukocytes and the formation of advanced glycation end products (AGEs) that eventually lead to the break-down of underlying connective tissue as well as alveolar bone.[5] Inflammatory and immunological mediators like IL-6 have indeed been reported to enhance bone resorption and osteoclastic activity in the saliva of chronic periodontitis patients.[6]

Salivary glucose degrades over time due to microbiological and enzymatic destruction and does not directly correlate with blood

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glucose, however glycated salivary proteins including fructosamine are reported to be even more consistent over time due to greater resilience against microbiological degradation.[7] Even though albumin is the most common blood protein and is regarded to be primarily a measure of glycated proteins, serum fructosamine consists of consequent ketoamine connections from glycation of serum proteins.[8] Serum fructosamine has been touted as a diagnostic aid, alone or in association with HbA1c, but unlike HbA1c, it indicates glycemic control over the past 2 weeks and displays short-term management of glycemic levels, which aids in earlier diagnosis of diabetes.[9] Substantial amounts of salivary fructosamine have also been linked to higher levels of hyperglycemia in research.[10]

According to statistics, >25% of patients were presumably clueless of their glycemic profile, and dental office acts as an appropriate environment for screening potential high-risk individuals with aberrant glucose levels.[11] Furthermore, saliva-based screening approaches are less intrusive, gingival crevicular fluid (GCF) all through periodontal evaluation earned great acceptance and tolerance among dental patients indicating patients' willingness to try other nontraditional approaches, especially if it excludes injection-related anxiety and added discomfort.[12] Additionally, monitoring glycemic state during a dental visit may be cost-effective, allowing for more extensive screening of high-risk individuals in the dental practice. Notably, a noninvasive and precise glycemic biomarker will greatly aid the medical field.[13] This noninvasive project may be seamlessly integrated with the dentist's office and then spread to all clinical settings once it has been thoroughly explored.

Therefore, the aim of the present study is to establish the relationship between salivary fructosamine and IL-6 in prediabetic patients with and without periodontitis and investigate if salivary fructosamine can be used as a noninvasive diagnostic tool in prediabetic patients with and without periodontitis.

Materials and Methods

Recruitment of Study Participants and Grouping

The current cross-sectional investigation was carried out in Department of Periodontology, A B Shetty Memorial Institute of Dental Sciences, NITTE Deemed to be University, Mangaluru, Karnataka, India, for duration of approximately 7 months (between August 2021 and February 2022) in which 36 participants (aged 30–55 years) volunteered.

- Group I—12 participants with self-reported systemically healthy and chronic periodontitis.
- Group II—12 medically diagnosed prediabetes patients with chronic periodontitis were recruited.
- Group III—12 medically diagnosed prediabetes patients without chronic periodontitis.

Ethical Guidelines

The Institutional Ethical Committee reviewed and approved the study protocol. Individuals who agreed to participate were instructed to read and sign a consent form.

Selection Criteria

Systemically healthy individuals with no history of prediabetes and chronic periodontitis were included in group I and individuals with medically diagnosed prediabetes RBS > 110 mg/dL and <170 mg/dL and HbA1C 5.7–6.4% were included under group II and individuals having plasma RBS < 110 mg/dL and <170 mg/dL and HbA1C < 5.7–6.4% were included in group III.[14] High-risk subjects who were 45 years and older, parents or siblings with type 2 diabetes, previous gestational diabetes were included in the study. Obese individuals (BMI > 30) with sedentary lifestyle along with periodontitis were subjected to screening for prediabetes. Subjects with gingival index score of 1–2 and interdental clinical attachment loss (CAL) ≥3 mm were considered as periodontitis subjects in groups I and II, and subjects with gingival index score <1 and interdental CAL < 3 mm were considered nonperiodontitis subjects in group III.[15] Patients with self-reported systemic illnesses, notably type 1 and type 2 diabetes, cardiovascular disorders, epilepsy, renal disorders, hepatic disorders etc., were excluded. Subjects under medications like nonsteroidal anti-inflammatory drugs, antibiotics, steroids, or any other drug known to influence periodontal tissues for the past 6 months, history of periodontal treatment in the past 6 months, presence of habits of smoking or pan chewing for the past 6 months or pregnancy and lactating women were also excluded from the study.

Clinical Periodontal Examination

A qualified examiner who was blind to the groups conducted the clinical periodontal examination. Probing depths (PD) were determined using William's graduated periodontal probe. BOP and Loe and Silness gingival index was determined and scored as score 0—normal gingiva, score 1—mild inflammation, slight change in color, slight edema, no BOP, score 2—moderate inflammation, moderate glazing, redness, edema, and hypertrophy, BOP, score 3—severe inflammation, marked redness and hypertrophy, ulceration and tendency to spontaneously bleed. Full mouth Russell's periodontal index (PI) according to PI criteria (0, 1, 2, 6, and 8) is based upon the signs of periodontitis and the sequence in which they usually appear, that is, inflammation, pocket formation, and loss of function. CAL was measured from gingival margin to base of the pocket. When recession of the gingival margin was present, the CAL was calculated by adding the PD to the gingival margin level. When the gingival margin is coronal to the cementoenamel junction, the CAL was calculated by subtracting the gingival margin level from the probing depth measured on all six surfaces of each tooth in both maxilla and mandible. A graded probe was used to quantify PD to the nearest millimeter. Chronic periodontitis was defined as CAL >/3 mm, and PD >/5 mm.

To Measure RBS and HbA1C

All patients were evaluated for serum RBS levels were assessed and presented in mg/dL, and serum HbA1C levels were determined, which were represented as percentages. Approximately 2.5 mL of venous blood was drawn from the arm and transferred into a sodium fluoride tube, and centrifuged for 5 minutes separating blood from plasma. Then the plasma was mixed with glucose diluent and fed into the machine. The RBS levels were confirmed, having followed the device's aspiration. Considering HbA1C, 2 mL of blood was transferred into an ethylenediaminetetraacetic acid tube and kept in the machine after mixing for 5 minutes. It was infused with diluents, and the aspirate was transmitted into the machine to obtain the results.

Collection of Unstimulated Whole Saliva Samples

At least 30 minutes prior to saliva collection, the individuals were advised to abstain from eating and drinking. The UWS samples were obtained as directed. In brief, all subjects ($n = 36$) were gently seated in a dental chair and instructed to expectorate 5 mL (without

swallowing) into uricol container over 5 continuous minutes. The UWS flow rate was measured in milliliters/minute and recorded. UWS samples were promptly frozen at −80°C following being placed on ice and aliquoted. Within 6 months after collection, UWS samples were evaluated for the levels of IL-6 and fructosamine by employing ELISA.

Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of IL-6 (kit from Diaclone) and fructosamine (kit from Bioassay Tech lab) in UWS samples from each patient. The ELISA kits used double antibody sandwich technique as its cornerstone. The manufacturer's instructions were followed while using the human IL-6 and fructosamine kits. The content of IL-6 and fructosamine correlated positively with the color depth. The absorbance and optical density of both IL-6 and fructosamine plates were evaluated employing a spectrophotometer at a wavelength of 450 nm. Also, IL-6 was scored at 6.25–200 pg/mL and fructosamine at 0.05–15 ng/mL according to the manufacturer's instructions.

Statistical Analysis

Statistical analysis was performed using SPSS version 2.0. Intragroup correlation between IL-6 and fructosamine levels between the three groups was assessed using Kolmogorov–Smirnov test. Intergroup comparison between salivary IL-6 and fructosamine levels between the three groups were assessed using the Chi-squared test. A *p*-values < 0.05 was considered significant. And $p < 0.001$ was considered very significant

Results

The present cross-sectional study had a sample that included 36 participants that consisted of 21 males (58.3%) and 15 females (41.6%) around the mean age group of 40.4 ± 1.7 years and divided into three groups according to the selection criteria.

The intragroup correlation between salivary IL-6 and fructosamine levels was statistically very highly significant in all three groups (Table 1). The mean salivary IL-6 and fructosamine levels for all 12 subjects were 47.8 ± 71.7 and 2.4 ± 1.1 in systemically healthy subjects with chronic periodontitis, 52.3 ± 73.0 and 2.0 ± 1.1 in prediabetic patients with chronic periodontitis and 17.8 ± 17.8 and 1.7 ± 0.8 in prediabetic patients without periodontitis, respectively, which were statistically very significant ($p < 0.001$) which sheds a light on the increase in the levels of glycated proteins like fructosamine and inflammatory markers like IL-6 in subjects with prediabetes with chronic periodontitis followed by systemically healthy subjects with chronic periodontitis and further decreased in prediabetic individuals without periodontitis.

The intergroup correlation for IL-6 and fructosamine levels between all three groups for the mentioned values was not statistically significant (Tables 2 and 3). The salivary values of inflammatory markers like IL-6 levels in prediabetic patients with chronic periodontitis were highest, followed by systemically healthy subjects with chronic periodontitis and prediabetic patients without chronic periodontitis. Also, the salivary values of fructosamine were highest in systemically healthy subjects with chronic periodontitis, followed by prediabetic patients with and without chronic periodontitis. Even though statistically not significant, the results infer that the glycated markers like fructosamine increase in the presence of chronic periodontitis even in systemically healthy subjects.

Discussion

Human saliva is actually referred to as the "mirror of the body" because it accurately reflects the physiological functioning of the body. Saliva is a vital biofluid that contains numerous biomarkers synthesized by the GCF, major and minor salivary glands, acquired pellicles, blood, as well as serum, shed from oral lacerations, bacterial products, desquamated epithelium, cellular components, food debris, and other viruses and fungi.[16] Saliva is also renowned as ultrafiltrate of plasma since it comprises over 190,00 unique peptide sequences and 100,0 different proteins. Biomarkers can

Table 3: Intergroup comparison between final salivary IL-6 and fructosamine levels

Group	*Test*	*Final value*
IL-6	Chi-squared Asymptotic Significant	1.075 0.584 nonsignificant
Fructosamine	Chi-squared Asymptotic Significant	2.348 0.309 nonsignificant

Table 1: Intragroup comparison between IL-6 and fructosamine levels

Sl. no.	*Group*	*N*	*Mean*	*Standard deviation*	*Z*
Group I	IL-6	12	47.888	71.730	3.406
	Fructosamine	12	2.488	1.148	$p < 0.001$ vhs
Group II	IL-6	12	52.389	73.026	3.580
	Fructosamine	12	2.039	1.123	$p < 0.001$ vhs
Group III	IL-6	12	17.859	17.836	4.158
	Fructosamine	12	1.794	0.890	$p < 0.001$ vhs

Table 2: Intergroup comparison between minimum and maximum salivary IL-6 and fructosamine levels

Group		*N*	*Mean*	*Standard deviation*	*Minimum*	*Maximum*
IL-6	Group I	12	47.888	71.730	1.440	241.070
	Group II	12	52.389	73.026	2.670	221.470
	Group III	12	17.859	17.836	3.990	57.270
Fructosamine	Group I	12	2.488	1.148	0.260	4.250
	Group II	12	2.039	1.123	0.390	3.500
	Group III	12	1.794	0.890	0.370	3.640

reach the saliva by extracellular ultrafiltration, passive diffusion, or active transport.[17]

Fructosamine's capacity to screen over a considerable time period makes it a possible and supportive criterion in determining the physiological status of a diabetic patient's periodontal tissues.[18] Salivary fructosamine, like plasma HbA1C levels, can be used to assess glycemic management during a 1–3 week period.[19] Moreover, IL-6 has also been shown to be a potential biomarker for the early diagnosis of type 2 diabetes mellitus (T2DM) as it enhances hepatic triglyceride secretion that has been associated with pathogenesis and inflammation of T2DM.[20]

In the present study, we aimed to evaluate fructosamine values in subjects without and with chronic periodontitis to establish the prevalence of prediabetes, as periodontitis has been considered a complication of prediabetes.[21] Several studies have attempted to establish a link between glycated proteins like fructosamine, salivary glucose, and other serum markers of disease. Kumar et al., examined the relationship between plasma fasting glucose, plasma HbA1C, and postprandial glucose among diabetic and nondiabetic individuals ($n = 50$). Patients with diabetes had higher levels of salivary fructosamine, plasma fasting, postprandial glucose and plasma HbA1C compared to nondiabetic individuals. Furthermore, salivary fructosamine levels showed a significant positive correlation with plasma fasting and postprandial glucose, as well as plasma HbA1C in both groups.[22]

The research paper is aimed at looking at the association of glycated proteins like fructosamine with proteins of inflammatory interest, like IL-6. We found elevated levels of fructosamine corresponding to increasing IL-6 levels. Significant relationships ($p < 0.001$) were established between chronic periodontitis and fructosamine as a criterion for diagnosing prediabetes. The results of the present study were supported by the studies conducted by Hong et al.,[23] who found the prevalence of chronic periodontitis to be 29% in patients with prediabetes.

The present study observed 24 prediabetic individuals in which proinflammatory markers like IL-6 increased in prediabetic conditions when compared to the control group. Hence the findings were consistent with the studies conducted by Shimazaki et al.,[24] that confirmed the positive relationship between hyperglycemia and periodontal disease, whereas studies conducted by Anoop et al., in which they included 120 hyperglycemic individuals under 35–60 years of age and categorized as normal, good diabetes control, average diabetes control, and poor diabetes control groups. A comprehensive periodontal examination was done, including parameters as oral hygiene index simplified, gingival bleeding index, and CAL. A very high percentage of prevalence of periodontitis was found in hyperglycemic individuals, which is in correlation with the findings of the study. However, gingival bleeding index was not found to vary with the worsening of glycemic status, which contradicted our findings.[25]

Although not statistically significant, mean values of fructosamine levels tended to be slightly lower in prediabetic subjects without periodontitis than in subjects with chronic periodontitis which are in consistent with the findings by Pontes Andersen et al.,[26] in which periodontitis was induced with ligatures in male adult Zucker fatty rats (ZFRs) and their lean littermates. After 4 weeks, body weight, food intake, glucose tolerance, insulin resistance, free fatty acids, cytokines, and alveolar bone loss were recorded. ZFRs with periodontitis, along with more bone loss, presented increased glucose intolerance that indicated prediabetes worsened periodontitis and periodontitis, in turn, was associated with deterioration of glucose metabolism in ZFRs. These findings suggested for diabetes as well as prediabetes that there seems to be a two-way relationship with chronic periodontitis. To the best of author's knowledge, this is the first study to compare biochemical markers like salivary fructosamine and chronic periodontitis in the screening of prediabetes

Sustained hyperglycemia can cause cellular damage through a variety of mechanisms, including increased generation of reactive oxygen species, protein kinase C, and AGEs, all of which are linked to inflammation and endothelial dysfunction.[27] The underlying processes of glucose metabolism worsening in prediabetic patients with chronic periodontitis, such as mediators, receptors, and other key molecules involved in this process, are concerns that need to be investigated further.[28]

The principal limitations of our study include the small sample size. Since the present study was cross-sectional, the effect of long-term glycemic control on periodontal destruction was not evaluated. Further studies are needed to assess the effect of individual glycemic control over a long time on salivary cytokine profiles among prediabetic patients as well as to determine if salivary fructosamine could be utilized as a marker for screening prediabetes in chronic periodontitis patients.

Conclusion

In line with previously published relevant data, our study adds to the growing body of evidence that the periodontal clinic is an excellent location for opportunistic prediabetes screening. It's worth looking into using point-of-care technology, such as fructosamine, as a noninvasive diagnostic technique for prediabetes. This improves practitioners' ability to contribute to the global effort to diagnose prediabetes and/or T2DM sooner.

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