Comparative evaluation of serum high-density lipoprotein and low-density lipoprotein levels and glycated hemoglobin levels and periodontal status in type 2 diabetic patients: A pilot project

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Abstract

Background: High levels of cholesterol in the body can be alarming and point toward a possible cardiac or diabetic problem. Current evidence reveals that the harmful low-density lipoproteins (LDL) cholesterol tend to increase in poorly controlled diabetes, whereas the useful high-density lipoprotein (HDL) cholesterol, known for its protective anti-inflammatory and antioxidant activities, is decreased. With a positive evidence of periodontal disease being implicated in diabetes, it was decided to investigate whether there was any association between serum HDL, LDL, glycated hemoglobin (HbA1c) and periodontal status with Type II diabetes mellitus patients.

Materials and Methods: A total of 500 nonsmoking patients (males and females) aged between 35 and 55 years with Type 2 diabetes mellitus and no other systemic disease were selected from the diabetic center, Diacon hospital, Bengaluru, Karnataka, India. Periodontal examination consisted of the clinical parameters, namely, attachment loss, gingival index (GI) and plaque index based on which the patients were divided into periodontally healthy and diseased groups. Blood samples were collected from each patient to evaluate the serum levels of HDL, LDL and HbA1c.

Results: No significant differences were observed between the HDL, LDL and HbA1c levels in both the periodontal groups ($P > 0.05$). Linear regression analysis showed significant positive correlations of clinical attachment level with LDL and negative correlation with HbA1c, whereas GI has a positive correlation with LDL and negatively with HDL and HbA1c levels ($P < 0.05$).

Conclusion: Varied associations were found between dyslipidemia, glycemic control and periodontal inflammation. Further longitudinal as well as interventional studies may be beneficial to ascertain the causal relationship between cholesterol levels, periodontal status and diabetes mellitus.

Keywords: Glycated hemoglobin, lipid profile, periodontitis, type 2 diabetes
INTRODUCTION

There is sufficient evidence available today to suggest that Type II diabetes mellitus (T2DM) is associated with an increased prevalence, extent and severity of periodontal disease. These two diseases have the capacity to induce an inflammatory response, leading to the production of various mediators of inflammation. Glycated hemoglobin/glycosylated hemoglobin (hemoglobin A1C, HbA1c) is formed in a nonenzymatic glycation pathway on exposure of hemoglobin to plasma glucose and serves as a marker for diabetic control. The HbA1c test provides an estimate of glycemic control over a period of approximately 2–3 months before the test, and the normal value is <6%. Evidence has linked the risk of developing periodontal disease to the levels of HbA1c, and the risk of elevations of HbA1c was associated with developing periodontal pockets of ≥4 mm.

On the other hand, Type I diabetes mellitus (T1DM) is known to alter lipid metabolism, and depending on the level of metabolic control of the disease, both quantitative and qualitative abnormalities in the lipid profile have been observed. Alternately, lower levels of serum high-density lipoprotein (HDL) have been observed in subjects with chronic periodontitis than in periodontally healthy subjects, and higher low-density lipoprotein (LDL) and triglyceride levels were reported in subjects with chronic periodontitis. An evident association between serum lipid profile and periodontal infection was further supported by longitudinal studies in which significantly decreased levels of serum LDL and total cholesterol were found after intensive periodontal treatment in severely affected periodontitis patients. Furthermore, a statistically significant increase in the level of HDL along with successful periodontal intervention has also been reported.

In spite of there being abundant literature on the associations between T1DM, lipid profiles and periodontal disease, till date, there is limited evidence on the associations between the serum lipid profile and periodontal inflammation in Type 2 diabetic patients. One of the early studies by Cutler et al. observed that gingival inflammation tended to increase with an increased level of serum triglycerides in Type 2 diabetic patients. Lim et al. reported that poor control of diabetes mellitus is associated with periodontal inflammation and LDL and total cholesterol, whereas no significant association was found between serum lipid profile (LDL, triglycerides and total cholesterol) and periodontal inflammation. Nassar et al. concluded that periodontal therapy led to improved lipid profiles in Type 2 diabetic patients, whereas Kalsi et al. concluded that in addition to effects on diabetes, periodontitis may contribute to elevated serum lipid levels and therefore potentially to systemic disease arising from chronic hyperlipidemia.

The present study was therefore carried out to investigate an association, if any, between HDL, LDL, glycated hemoglobin and periodontal status in patients with T2DM.

MATERIALS AND METHODS

Following the approval from the institutional ethical committee (IEC NO-VEF/23052011), a total of 505 patients from Diacon hospital, Bengaluru, aged between 35 and 55 years with T2DM noninsulin-dependent diabetes mellitus were included after obtaining consent to participate in the study. Patients on insulin therapy, any other systemic disease or condition and smokers were excluded. Patient records from the hospital were used to retrieve data regarding the diabetic state and general health status of the subjects with details of blood investigations evaluating HDL, LDL and HbA1C recorded separately. Glycated hemoglobin (HbA1c) was analyzed using high performance liquid chromatographic technique. HDL and LDL were separated using ultracentrifugation method.

In addition, the clinical parameters, i.e., gingival index (GI), plaque index (PI), probing pocket depth (PPD) and clinical attachment level (CAL), were measured using UNC-15 periodontal probe. Based on the clinical periodontal parameters, the study population was divided into 2 groups based on the findings obtained on the periodontal parameters. Patients with GI and plaque scores under 1 with no probing depths and CAL were grouped under periodontally healthy, whereas those with GI and PI over 1 with evidence of probing depth and CAL were grouped under periodontal disease.

- Periodontally healthy: No gingival or periodontal disease
- Periodontitis: With periodontal disease.

Statistical analysis

Statistical analyses were performed using statistical software IBM SPSS Statistical Package for the Social Sciences, version 22 (IBM, Chicago, Illinois, USA) for Windows. Unpaired t-tests were used to compare the HDL, LDL and HbA1C values between the two groups. Linear regression analysis was carried out to establish any association between the parameters, and the level of statistical significance was set at <5% (P < 0.05). All analyses were based on subject level data.

RESULTS

The subject characteristics were presented as

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mean values (± standard deviation) per subject or frequency [Table 1]. Although the mean HDL and LDL values were higher in the periodontally healthy group compared to the diseased group, the differences were not statistically significant (P > 0.05) [Tables 2 and 3]. Similarly, there were no significant differences in the glycated hemoglobin levels in both the groups (P > 0.05), although the mean values in the periodontitis group were higher than the periodontally healthy group [Table 4].

Linear regression analysis showed a significant positive association between CAL and PPD (r² = 0.483) and CAL and LDL levels (r² = 0.134) and a significant negative association between CAL and glycated hemoglobin (HbA1C) levels (r² = −0.133) (P < 0.05) [Table 5].

A significant negative association was found between GI scores and HDL levels (r² = −0.233) and GI scores and glycated hemoglobin (HbA1C) levels (r² = −0.119) (P < 0.05) and a significant positive correlation was found between GI scores and LDL levels (r² = 0.132) (P < 0.05) [Table 6]. Similarly, a significant positive correlation was observed between PI scores and HDL levels (r² = 0.127) (P < 0.05) [Table 7].

**DISCUSSION**

The association between dyslipidemia, characterized by a reduction in serum HDL level, and periodontal inflammation has been suggested in a number of earlier studies[5-8,13] HDL is said to have a protective association with periodontal inflammation by regulating the inflammatory processes via several key mechanisms. HDL has also been found to be effective in binding and neutralizing lipopolysaccharide of Gram-negative bacteria, thereby limiting the expression of cytokines and lipid peroxidation.[19,20] Except for the qualitative abnormalities of lipoproteins in T1DM, serum triglycerides and LDL tend to increase in poorly controlled diabetes, whereas the level of HDL tends to decrease.[17,18] In addition, the level of glycemic control is associated with periodontal inflammation.[3,21]

As a combined occurrence, researchers have also suggested that the decreased diabetic control in Type 2 diabetes may influence the increased serum triglycerides and periodontal health.[15-18,22] Al-otaibi et al. have suggested that dyslipidemia may be a possible link between periodontal disease and diabetes mellitus.[23]

With such diverse and complex associative evidence between the three chronic conditions, namely, dyslipidemia, diabetes and periodontal disease, the present study was attempted to investigate a possible association present between serum HDL, LDL, glycated hemoglobin and periodontal status in Type II diabetes mellitus patients.

The study population comprising 505 patients had an average age of 46.65 ± 6.83 with nearly equal number of males and females. The severity of periodontitis (periodontitis...
Table 6: Association between gingival index and associated explanatory variables using linear regression analysis

| Variable | B     | 95% CI for B | P     | r²  |
|----------|-------|--------------|-------|-----|
| Age      | 0.001 | −0.003-0.006 | 0.545 | 0.027 |
| PI       | 0.53  | −0.088-0.194 | 0.462 | 0.033 |
| PPD      | 0.053 | −0.038-0.144 | 0.255 | 0.051 |
| HDL      | −0.008 | −0.012−0.005 | 0.000* | −0.233 |
| LDL      | 0.002 | 0.001-0.003 | 0.003* | 0.132 |
| HbA1c (%)| −0.021 | −0.036−0.006 | 0.000* | −0.119 |

*P < 0.05 is significant. PI: Plaque index, PPD: Probing pocket depth, HDL: High-density lipoprotein, LDL: Low-density lipoproteins, CI: Confidence interval, HbA1c: Glycated hemoglobin

Table 7: Association between plaque index and associated explanatory variables using linear regression analysis

| Variable | B     | 95% CI for B | P     | r²  |
|----------|-------|--------------|-------|-----|
| Age      | −0.001 | −0.004-0.002 | 0.683 | −0.018 |
| PPD      | 0.002 | −0.055-0.059 | 0.950 | 0.003 |
| HDL      | 0.003 | 0.001-0.005 | 0.004* | 0.127 |
| LDL      | 0.000 | 0.000-0.001 | 0.144 | 0.066 |
| HbA1c (%)| −0.009 | −0.018-0.001 | 0.084 | −0.077 |

*P < 0.05 is significant. PPD: Probing pocket depth, HDL: High-density lipoprotein, LDL: Low-density lipoproteins, CI: Confidence interval, HbA1c: Glycated hemoglobin

...group) was high with CAL values over 5 mm. The mean HDL and LDL levels of the study group were reported as 44.45 ± 10.74 and 96.41 ± 32.13, respectively. Ying Ouyang et al. [24] reported that HDL levels <40 mg/dl (corresponding to levels <1.04 mmol/l) have been considered an independent risk factor for coronary heart disease, whereas at levels ≥60 mg/dl (corresponding to levels ≥1.55 mmol/l), there may be a reduced risk. The mean glycated hemoglobin level was 8.70 ± 2.19, which was definitely high, reflecting on the poor glycemic control of the patients.

The HDL and LDL values were comparatively higher in the periodontally healthy group compared to the diseased group, although the results were not statistically significant, which were in accordance with Gita et al. [25] who found that there was no association among periodontal disease and the levels of total cholesterol, LDL, HDL and triglycerides. However, a significant positive correlation was observed between periodontal attachment loss and gingival inflammation with LDL levels, thereby indicating that there may be a possible association between periodontal disease and dyslipidemia. Sharma et al. [26] showed that high serum LDL cholesterol may be associated with periodontitis in healthy people. However, it is unclear whether periodontitis causes an increase in the levels of serum LDL or an increased LDL is a risk factor for both periodontitis and cardiovascular disease. Katz et al. [27] found that the presence of periodontal pockets as measured by community periodontal index for treatment needs (CPITN) was positively associated with total cholesterol and LDL cholesterol and the findings of the study support the reports linking increased prevalence of cardiovascular mortality among patients with periodontal disease.

Our study also found a significant negative correlation between gingival inflammation and HDL and a significant positive correlation of PI with HDL. These findings are complex to substantiate, as a study by Passoja et al. [27] also found a negative association between serum HDL and periodontal inflammation, whereas Heinrichs and Desvarieux [28] found a positive one; however, several others found no significant association between HDL levels and periodontal disease. [25,28] However, Passoja et al. controlled the most important confounding factors and concluded that serum HDL level may be regarded as a marker of susceptibility to periodontal inflammation and suggested that the anti-inflammatory and anti-infective functions of HDL cholesterol must be considered to verify a possible causal relationship between serum HDL and periodontal inflammation in a longitudinal study. [27]

There were no significant differences between the healthy and periodontitis group with regard to glycated hemoglobin, although the mean HbA1C levels were higher in the periodontitis group. However, a significant negative correlation was found between HbA1c levels and CAL as well between HbA1c levels and gingival inflammation. Nevertheless, these findings are statistical outcomes and may or may not align with evidence which concluded that patients having poor glycemic control had more severe periodontitis as compared to patients having a fair one [31] and also that the level of glycemic control as measured by HbA1c is the most consistent risk factor associated with the extent and severity of periodontal disease [16].

The focus of our study was on the combined association of HDL, LDL, HbA1c levels and the periodontal status and linear regression analysis showed that the severity of periodontal disease (CAL) was positively correlated with LDL while showing a negative one with HbA1c and none with HDL, whereas the parameters of periodontal inflammation (GI and PI) were negatively correlated with HDL and HbA1c while being positively correlated with LDL levels (GI) with only PI being positively correlated with HDL levels. These correlations although diverse from other evidence, suggest varied associations between lipid levels, glycemic control and periodontal disease in T2DM. Passoja et al. found a negative association between periodontal inflammation and serum HDL level in subjects with TIDM and also that an association between periodontal inflammation and serum LDL level was evident and even stronger after considering the potential confounding effect of the IL-6 _174 genotype (GG...
vs. GC/CC) of the subjects.\textsuperscript{[27]} However, analogous to cardiovascular diseases, in which the antioxidant and anti-inflammatory activities of HDL are associated with protection against inflammation,\textsuperscript{[32]} high HDL levels were associated with fewer inflamed periodontal sites in our study. Nepomuceno et al\textsuperscript{[23]} observed that dyslipidemia patients also affected by poorly controlled diabetes presented increased severity of periodontitis, collectively negatively affecting health and quality of life. They further concluded that dyslipidemia appears to be the primary disease that is associated with gene expression of immune-related genes, while parameters of T2DM and periodontal disease were correlated with the expression of these important immune genes. Hyperlipidemia may persist even in subjects with good glycemic control\textsuperscript{[34]} and elevations in serum lipids may be more important, and much more destructive than the glycemic state.\textsuperscript{[16,35,36]}

Although we excluded an important risk factor such as smoking, our study could establish a noteworthy association between periodontal inflammation, disease severity and lipoproteins (positive with LDL and negative with HDL), and in addition, a negative one with HbA1c. Nevertheless, the exact nature of this connection is still elusive and it may not be possible to draw concrete conclusions.

**CONCLUSION**

Within the limitations of the study, the mean HDL, LDL and HbA1c levels were higher in the periodontally diseased group. However, the precise nature of the association is inconclusive. Perhaps, longitudinal studies verifying the cause-and-effect relationship between these parameters may aid in providing a definite inference. Additionally, including a nondiabetic control group with periodontal disease would have allowed us to have a better understanding on the influence of diabetes mellitus on the association between serum lipid levels and the extent of periodontal inflammation.

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**Conflicts of interest**

There are no conflicts of interest.

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