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Serum high-density lipoprotein cholesterol level associated with the extent of periodontal inflammation in type 1 diabetic subjects

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Abstract

Aim: High-density lipoprotein (HDL) cholesterol is known for its anti-inflammatory and antioxidant activities in protection against cardiovascular diseases. We investigated whether a protective association also exists between serum HDL and periodontal inflammation in type 1 diabetic subjects (T1DM).

Methods: Plaque and periodontal inflammation (bleeding and PD $\geq$ 4 mm) were examined in 80 subjects with T1DM. The serum levels of glycosylated haemoglobin (HbA1c, %) and HDL (mmol/l) were determined. Adjusted associations between inflammation and serum HDL were analysed using linear regression analysis. To study the linearity of the association, the subjects were categorized into HDL tertiles (I-III).

Results: A statistically significant negative association was observed between serum HDL level and the extent of bleeding and PD $\geq$ 4 mm. Subjects in HDL tertiles II and III (high HDL) presented significantly fewer inflamed sites when compared with the subjects in tertile I (low HDL), whereas no significant difference in the number of inflamed sites was observed between tertiles II and III.

Conclusions: Based on the finding of a negative association between serum HDL and periodontal inflammation, HDL may be considered a marker of susceptibility to periodontal inflammation. A longitudinal study is needed to verify possible causal relationship between serum HDL and inflammation.

Key words: high-density lipoprotein cholesterol; inflammation; periodontitis; type 1 diabetes mellitus

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Conflict of interest and source of funding statement

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The causative agents in chronic periodontitis are pathogens, mainly Gram-negative bacteria, which inhabit subgingival biofilms (Sockransky & Haffajee 2005), but the initiation and progression of the disease are determined by immune inflammatory responses of the host. A number of earlier studies have indicated that the serum lipid profile may be associated with inflammatory host responses. Accordingly, microbial infections, such as those caused by *Chlamydia pneumoniae* and *Helicobacter pylori*, have been reported to alter the serum lipid profile by

decreasing the HDL level and the ratio of HDL to total cholesterol and increasing serum triglyceride and total cholesterol levels (Laurila et al. 1997, 1999). As regards periodontal infection, lower levels of serum HDL have been observed in subjects with chronic periodontitis than in periodontally healthy subjects (Buhlin et al. 2003, Craig et al. 2003, Nibali et al. 2007, Monteiro et al. 2009). On the other hand, higher low-density lipoprotein (LDL) and triglyceride levels were reported in subjects with chronic periodontitis (Katz et al. 2002, Craig et al. 2003, Nibali et al. 2007, Monteiro et al. 2009). 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 (D'Aiuto et al. 2005, 2006). Furthermore, a statistically significant increase in the level of HDL along with successful periodontal intervention has been reported (Pussinen et al. 2004a, b, Buhlin et al. 2009).

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 (Vergés 2009). Only a few studies on the associations between the serum lipid profile and periodontal inflammation in diabetic patients are available. Lim et al. (2007) 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, total cholesterol) and periodontal inflammation. According to Cutler et al. (1999), gingival inflammation tended to increase with an increasing level of serum triglycerides in type 2 diabetic patients.

A number of studies have shown a strong inverse correlation between cardiovascular diseases and HDL cholesterol (McGrowder et al. 2011). The protective association is based on the antioxidant and anti-inflammatory activities of HDL (Ansell et al. 2005). Using an analogous starting point, one could hypothesize that the protective influence of HDL could also be seen in other inflammatory conditions such as chronic periodontitis. Therefore, our aim was to investigate the association between serum HDL level and periodontal inflammation using the extent of sites with bleeding and PD $\geq$ 4 mm as the outcome and adjusting for obvious confounding factors. Due to the already known association between the interleukin (IL)-6^{-174} genotype and periodontal infection in the present subjects (Raunio et al. 2009) and an evident influence of IL-6^{-174} genotype on the lipid profile in general (Fernández-Real et al. 2000, Henningsson et al. 2006, Riikola et al. 2009), we also considered the possible confounding effect of this genotype in the studied associations. Using this kind of a setting we aimed to add to the information obtained in previous studies in which periodontal infection has been used as a determinant of the serum lipid profile.

Material and Methods

Subjects

The material of the present study was comprised of a total of 80 patients of Caucasian origin with type 1 diabetes mellitus (T1DM) (Raunio et al. 2009). All the subjects were examined by an experienced periodontal specialist (T.R.) at the Specialist Dental Health Care Unit, City of Oulu, Oulu, Finland, following a detailed calibration of the clinical examination procedure. Informed consent was obtained from all the subjects and the study protocol was approved by the Ethical Committee of Oulu University Hospital, Oulu, Finland. Subjects needing prophylactic antibiotic medication in association with periodontal probing as well as those with immunosuppressive medication or antibiotics during the past 4 months were excluded from the study. Patient records were used to retrieve data regarding the diabetic state and general health status of the subjects. The mean time since the diagnosis of T1DM and, consequently, the duration of insulin therapy was 19.9 years (range: 1.2–48.0 years, median 18.3 years). A total of 72 subjects were on both long-acting and rapid acting insulin. Use of both long- and short acting insulin was recorded for six subjects. One subject was on long-acting insulin only and one used both mixed and short acting insulin. Three subjects were on insulin pump therapy. Statin (atorvastatin, pravastatin or simvastatin) had been prescribed to 19 subjects. Data concerning smoking habits were obtained by interviewing the subjects in conjunction with the clinical examination and the subjects were categorized as smokers and non-smokers. There were altogether 24 smokers, and of these 15 smoked either occasionally or <10 cigarettes per day and nine subjects smoked $\geq$10 cigarettes per day. The subjects' body mass index (BMI, kg/m^2) and age were also recorded.

Clinical periodontal examination

Clinical measurements were made on four surfaces (mesiobuccal, midbuccal, distobuccal, and midlingual) of each tooth, excluding third molars. After gentle drying with air, the presence of visible plaque was assessed according to the criteria of scores 2 and 3 of the plaque index (Silness & Löe 1964). A ball-pointed periodontal probe with 2 mm graduations was used to measure probing depth (PD) from the gingival margin to the base of the crevice/pocket. A positive score for bleeding on probing (BOP) was registered if a site presented bleeding 20–30 s after probing. The extent of periodontal inflammation was expressed as the number of sites with a positive score for bleeding and PD $\geq$ 4 mm (Table 1).

Laboratory assays

A venous blood sample was drawn from each subject on the day of the examination. Glycosylated haemoglobin (HbA1c, %) was analysed after sampling using a latex immunoturbidimetric method (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). The serum samples were stored at −70°C until assayed. The levels of serum HDL and LDL cholesterol (mmol/l) were measured using direct enzymatic methods implemented in the ADVIA Chemistry 2400 system (Siemens Medical Solutions Diagnostics). Serum

Table 1. Subject characteristics presented as mean values (±SD) and numbers of subjects

Parameter	
Age (years)	38.6 ± 12.3
Gender (female/male)	46/34
Smoking (non-smoker/smoker)	56/24
IL-6^{-174} genotype (GG/GC,CC)	17/63
Number of	
Teeth	25.7 ± 4.1
Sites	102.9 ± 16.5
Number of sites with	
Plaque	30.7 ± 22.3
Bleeding and PD ≥ 4mm	23.1 ± 18.5
Duration of DM, years	19.9 ± 11.9
HbA1c (%)	8.5 ± 1.4
HDL (mmol/l)	1.5 ± 0.4
LDL (mmol/l)	2.3 ± 0.8
Triglycerides (mmol/l)	1.3 ± 0.7
BMI (kg/m^2)	24.7 ± 3.3

HbA1c (%), glycosylated haemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index.

triglyceride level was determined using enzymatic and photometric methods of the same system.

Genotyping of IL-6^{-174}

The patients' DNA was extracted from an EDTA blood sample, and the IL-6^{-174} genotype was tested using a polymerase chain reaction (PCR) as described previously by Tervonen et al. (2007).

Statistical methods

Statistical analyses were performed using statistical software (SPSS Statistical Package for Social Sciences, version 16.0 for Windows; SPSS Inc., Chicago, IL, USA) and the level of statistical significance was set at <5% ($p < 0.05$). All analyses were based on subject-level data on the number of sites with bleeding and PD ≥ 4 mm. The subject characteristics are presented as mean values (±SD) per subject or frequencies of subjects (Table 1). Linear regression analysis was used to determine the adjusted associations between the number of inflamed sites (the outcome variable) and serum HDL level (the main explanatory variable). Adjustments were made for HbA1c (%), age, gender, smoking, number of sites with plaque, number of measured sites (Tables 2 and 6) and the IL-6^{-174} genotype (Table 6). In separate analyses, we also controlled for duration of T1DM, statin medication and BMI. To further explore the association between serum HDL level and periodontal inflammation, we divided the subjects into tertiles I –III according to ascending level of serum HDL (Tables 3 and 4). A linear regression model was also used in studying the adjusted associations between serum HDL level and the number of sites with bleeding, and PD ≥ 4 mm (the outcome variables), and the IL-6^{-174} genotype (Table 5).

Table 2. Adjusted associations between the number of sites with bleeding and PD ≥ 4 mm (the outcome variable) and associated explanatory variables using linear regression analysis

	B	95% CI for B	*p*-value
HDL (mmol/l)	**−9.72**	**−18.0 to −1.44**	**0.022**
HbA1c (%)	**2.90**	**0.45 to 5.36**	**0.021**
Age	**0.34**	**0.02 to 0.66**	**0.037**
Male gender	−1.71	−9.12 to 5.70	0.647
Non-smoker	**−10.97**	**−18.51 to −3.44**	**0.005**
Number of sites with plaque	**0.40**	**0.24 to 0.55**	**< 0.001**
Number of measured sites	0.16	−0.09 to 0.40	0.212

Adjusted for continuous variables: HbA1c (%), age, number of sites with plaque and number of measured sites and categorized variables; gender: males *versus* females (reference group), smoking: non-smokers *versus* smokers (reference group).
PD, pocket depth; HDL, high-density lipoprotein cholesterol; HbA1c (%), glycosylated haemoglobin A1c.
Bold face denotes statistical significance.

Results

The subjects' characteristics are presented in Table 1. The mean level of HbA1c of the present subjects was 8.5% (±1.4) and of serum HDL, 1.5 mmol/l (±0.4). Twenty-four subjects (30%) reported to be smokers. Seventeen subjects (21%) carried the GG genotype of IL-6^{-174}. On average, 31 sites per subject harboured plaque and 23 sites, bleeding and PD ≥ 4 mm.

Plaque, HbA1c level, age, gender and smoking status were associated with the number of sites with bleeding and PD ≥ 4 mm. After adjusting for them and the number of measured sites, a statistically significant negative association was found between the number of sites with bleeding and PD ≥ 4 mm and serum HDL level (B = −9.72, p = 0.022) (Table 2). As BMI, total cholesterol, LDL and triglycerides were not associated with the number of sites with bleeding and PD ≥ 4 mm (r^2 = 0.009, r^2 = −0.113, r^2 =−0.007, r^2 = −0.010, respectively) they were not included in the model. No essential changes in the association between serum HDL level and periodontal inflammation were observed, when duration of DM or statin medication was added into the model. In addition, using a separate model, we showed that there was no significant interaction between smoking and serum HDL.

To further explore the association between serum HDL level and periodontal inflammation, we divided the subjects into tertiles I–III according to ascending level of serum HDL (Table 3). Except for the higher number of females in tertile III, no essential between-tertile differences in subject characteristics could be observed. The unadjusted mean number of sites with bleeding and PD ≥ 4 mm were 31.2, 18.8, and 19.2 in tertiles I, II, and III, respectively. The adjusted associations between the number of sites with bleeding and PD ≥ 4 mm and serum HDL indicated that while the subjects in tertile II and III presented significantly fewer sites with bleeding and PD ≥ 4 mm when compared with the subjects in tertile I (p = 0.046 and p = 0.002, respectively), no significant difference in the number of such sites was observed between tertiles II and III (p = 0.272) (Table 4).

Based on our data, the IL-6^{-174} genotype turned out to be a confounding factor in the association between periodontal inflammation and serum HDL level. Accordingly, subjects with the GG genotype pre-

Table 3. Subject characteristics in the serum HDL tertiles

HDL tertiles (limits)	*n*	Age (mean, 95% CI)	Smokers (*n*)	Females (*n*)	Number of teeth (mean, 95% CI)	Plaque (mean, 95% CI)	Bleeding and PD $\geq$ 4 mm (mean, 95% CI)
Tertile I (0.57–1.35 mmol/l)	27	39.9 (35.9, 44.3)	7	13	25.9 (24.3, 27.5)	33.7 (25.0, 42.4)	31.2 (21.9, 40.4)
Tertile II (1.36–1.69 mmol/l)	27	37.2 (32.4, 42.1)	10	13	24.9 (22.8, 27.0)	26.8 (17.3, 36.3)	18.8 (13.4, 24.3)
Tertile III (1.70–2.92 mmol/l)	26	38.6 (33.1, 44.0)	7	20	25.7 (24.8, 26.6)	30.7 (23.3, 40.2)	19.2 (13.4, 25.0)

PD, pocket depth; HDL, high-density lipoprotein cholesterol.

Table 4. Associations between the number of sites with bleeding and PD $\geq$ 4 mm (the outcome variable) and serum HDL (classified into tertiles) using linear regression analysis

HDL	*n*	B (95% CI for B)	*p*-value
Tertile I (0.06–1.35 mmol/l)	27	Reference	
Tertile II (1.36–1.69 mmol/l)	27	**−8.13 (−16.09 to −0.17)**	**0.046**
Tertile III (1.70–2.92 mmol/l)	26	**−12.74 (−20.57 to −4.91)**	**0.002**
Tertile II	27	Reference	
Tertile III	26	−4.61 (−12.90 to 3.69)	0.272

Adjustments made for HbA1c (%), age, gender, smoking, number of sites with plaque and number of measured sites.
PD, pocket depth; HDL, high-density lipoprotein cholesterol.
Bold face denotes statistical significance.

Table 5. Adjusted associations between the IL-6^{-174} genotype and serum HDL level (mmol/l) (*Model I*), and the IL-6^{-174} genotype and the number of sites with bleeding and PD $\geq$ 4 mm (*Model II*)

	B	95% CI for B	*p*-value
Model I			
HDL (the outcome)	**0.32**	**0.09–0.55**	**0.007**
GG genotype of IL-6^{-174}			
Model II			
Bleeding and PD $\geq$ 4mm (the outcome)	**10.62**	**2.22–19.02**	**0.014**
GG genotype of IL-6^{-174}			

Model I: adjusted for HbA1c (%), gender, smoking, number of sites with bleeding and PD $\geq$ 4 mm, and number of measured sites. *Model II*: adjusted for HbA1c (%), age, gender, smoking, number of sites with plaque, and number of measured sites.
IL-6^{-174} genotype: GG *versus* GC/CC (reference group).
PD, pocket depth; HDL, high-density lipoprotein cholesterol; HbA1c (%), glycosylated haemoglobin A1c.
Bold face denotes statistical significance.

Table 6. Adjusted associations between the number of sites with bleeding and PD $\geq$ 4 mm (the outcome variable), and serum HDL level (mmol/l) and IL-6^{-174} genotype (the main explanatory variables) using linear regression analysis

	B	95% CI for B	*p*-value
HDL (mmol/l)	**−12.76**	**−20.72 to −4.79**	**0.002**
GG genotype of IL-6^{-174}	**13.59**	**5.46 to 21.71**	**0.001**
HbA1c (%)	**2.45**	**0.14 to 4.77**	**0.038**
Age	0.26	−0.04 to 0.56	0.086
Male gender	−5.12	−12.35 to 2.11	0.162
Non-smoker	**−11.51**	**−18.58 to −4.45**	**0.002**
Number of sites with plaque	**0.38**	**0.23 to 0.52**	**< 0.001**
Number of measured sites	0.15	−0.09 to 0.38	0.213

Adjusted for HbA1c (%), age, number of sites with plaque and number of measured sites as continuous variables and IL-6^{-174} genotype: GG *versus* GC + CC (reference group), gender: males *versus* females (reference group), smoking: non-smokers *versus* smokers (reference group).
PD, pocket depth; HDL, high-density lipoprotein cholesterol; HbA1c (%), glycosylated haemoglobin.
Bold face denotes statistical significance.

sented significantly higher serum HDL levels (*Model I*) and significantly higher numbers of sites with bleeding and PD $\geq$ 4 mm (*Model II*) than those with the CG/CC genotype (Table 5). After adding the IL-6^{-174} genotype into the original model (Table 2), even stronger associations between the number of sites with bleeding and PD $\geq$ 4 mm and serum HDL ($B = -12.76$, $p = 0.002$) were observed (Table 6). However, no interaction between the IL-6^{-174} genotype and serum HDL was

observed (separate model, data not shown).

A significant negative association between the number of sites with bleeding and PD $\geq$ 4 mm and serum HDL was also found in non-smokers ($B = -9.86$, 95% CI for B, -19.62 to -0.09, $p = 0.048$) when adjustments were made for the level of HbA1c, age, gender, the IL-6^{-174} genotype, number of sites with plaque and number of measured sites.

Discussion

The principal finding of the present study was a negative association between periodontal inflammation and serum HDL level in subjects with T1DM. Another important finding was that the association between periodontal inflammation and serum HDL level was evident and even stronger after considering the potential confounding effect of the IL-6^{-174} genotype (GG *versus* GC/CC) of the subjects.

Dyslipidemia, characterized by a reduction in serum HDL level, has been associated with periodontal inflammation in a number of earlier studies (Buhlin et al. 2003, Craig et al. 2003, Pussinen et al. 2004b, Nibali et al. 2007, Monteiro et al. 2009). However, whereas most previous studies have focused on the effect of periodontal inflammation and/or microbes on the serum lipid profile, we applied an opposite analysis strategy using periodontal inflammation as the outcome and serum HDL level as the main explanatory variable in the statistical analyses. Due to the cross-sectional nature of our study, definite conclusions of a causal relationship between the extent of periodontal inflammation and serum HDL level cannot be drawn. However, analogous to cardiovascular diseases, in which the antioxidant and anti-inflammatory activities of HDL are associated with protection against inflammation (McGrowder et al. 2011), high HDL levels were associated with fewer inflamed periodontal sites in the present T1DM subjects. Moreover, our findings parallel previous studies in which other complications of diabetes mellitus, such as retinopathy (Sasongko et al. 2011) or microalbuminuria (Mattock et al. 2001), were associated with decreased plasma HDL or ApoAI, a main constituent of HDL cholesterol.

HDL is known to regulate the inflammatory processes via several key mechanisms, allowing us to draw conclusions of its protective association with periodontal inflammation. Namely, lipoproteins, and particularly HDL, have been found to be effective in binding and neutralizing lipopolysacharide (LPS) of Gram-negative bacteria, thereby limiting the expression of cytokines and lipid peroxidation (Levine et al. 1993, Nofer et al. 2002). In addition, HDL is known to inhibit LDL-induced monocyte chemotactic activity in arterial wall co-cultures (Navab et al. 1991). In cardiovascular diseases, the antiatherogenic function of HDL relates to its ability to promote the efflux of excess cholesterol by macrophages and non-macrophages and return it to the liver for excretion (reverse cholesterol transport) (Barter & Rye 1996). HDL is also considered to have an antioxidant feature; treatment of human endothelial cells with HDL or apoA-I converted cells unable to oxidize LDL (Navab et al. 2000). Despite the overwhelmingly anti-inflammatory activity of HDL in normal conditions, the protective character of HDL during systemic inflammation can diminish to a point where it becomes pro-inflammatory (Fogelman 2004). It has been suggested that inflammation damages the apoA-1 of HDL and leads to a reduction in its amount and also in paraoxonase, an anti-inflammatory enzyme associated with HDL (Zheng et al. 2004, Boemi et al. 2001). Thus, the protective role of HDL may be related not only to the level, but also to the quality of HDL (Khera et al. 2011). Supporting the previous, Pussinen et al. (2004a) showed in an *in vitro* study that HDL-mediated cholesterol efflux tended to be higher after periodontal treatment, suggesting improved protective capacity of HDL after elimination of infection. As regards the level of HDL and the risk for systemic inflammatory diseases, 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 $\geq$60 mg/dl (corresponding to levels $\geq$1.55 mmol/l) a reduced risk has been reported (Oyang et al. 2011). Based on the categorization of our subjects into HDL tertiles, the protective association of HDL with periodontal inflammation was evident at levels $\geq$1.35 mmol/l. According to current guidelines, the target level of HDL recommended in Finland is $\geq$1.0 mmol/l.

Glycemic control of diabetes (HbA1c), smoking and plaque were considered to be confounding factors in the association between periodontal inflammation and serum HDL, and therefore corresponding adjustments were made in the multiple regression models. 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 (Guy et al. 2009, Weidman et al. 1982). On the other hand, the level of glycemic control is associated with periodontal inflammation (Taylor 2001). It should be pointed out, however, that despite controlling for the level of glycemic control and also for the duration of DM, there may be some residual confounding that influences the strength of the observed association. Also, smoking is known to decrease the serum HDL level (reviewed by Maeda et al. 2003), and its influence on the severity of periodontal disease is well reported (Bergström 2006). In addition to adjusting for smoking in the regression model, we disclosed that there was no significant interaction between smoking and HDL and that the association between serum HDL and the extent of periodontal inflammation was significant also in non-smokers. As shown by Pussinen et al. (2004a), periodontal pathogens may affect the protective characteristics of HDL. By controlling for plaque, we could demonstrate that the association between periodontal inflammation and serum HDL existed independently of the microbial load. Statins are known to possess anti-inflammatory activity (Jain & Ridker 2005), and Saxlin et al. (2009) previously suggested that statin medication may have a protective effect on periodontal inflammation. Despite this, we disclosed that the association between serum HDL and periodontal inflammation existed

independently of statin medication, as well. It should also be kept in mind that, beyond the frame of this study, there may be some other factors that affect the HDL level without affecting the extent of periodontal inflammation.

As shown previously, the IL-6^{-174} genotype (GG *versus* GC/CC) may have some influence on the lipid profile. Women carrying the GG/GC genotype of IL-6^{-174} have been reported to present significantly higher serum levels of total and LDL cholesterol and triglycerides compared with women carrying the CC genotype (Henningsson et al. 2006). In another study serum total and LDL cholesterol levels were significantly higher in male subjects carrying the GG/GC genotype of IL-6^{-174}, and a trend towards a higher HDL level in male subjects carrying the same genotype was observed (Riikola et al. 2009). To our knowledge, this is the first study in which the confounding effect of the IL-6^{-174} genotype (GG *versus* GC/CC) on the association between periodontal inflammation and HDL level has been taken into account. However, the possible causal pathways remain unclear.

Methodological limitations of this study include a fairly small sample size and a lack of power analysis for the sample size neither was there any characterization of the qualitative features of HDL. Also, by using biochemical or microbiological markers of inflammation, we would have been able to better characterize the activity of periodontal inflammation. Including a non-diabetic control group with a similar degree of periodontal inflammation would have allowed us to draw conclusions on the influence of diabetes mellitus on the association between serum HDL level and the extent of periodontal inflammation. However, considering our controlling for the most important confounding factors, the present results indicate that serum HDL level may be regarded as a marker of susceptibility to periodontal inflammation. Considering the anti-inflammatory and anti-infective functions of HDL cholesterol, it is necessary to verify a possible causal relationship between serum HDL and periodontal inflammation in a longitudinal study.

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Clinical Relevance

Scientific rationale for the study: HDL cholesterol is known for its anti-inflammatory and antioxidant properties. In this study, we explored whether any association exists between serum HDL cholesterol level and the extent of periodontal inflammation in subjects with T1DM.

Principal finding: A statistically significant, non-linear, negative association was found between the extent of sites with bleeding and PD $\geq$ 4mm and serum HDL level.

Practical implications: The protective association between serum HDL and periodontal inflammation evidently implies that serum HDL may be considered a marker of susceptibility to periodontal disease.