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Plasma lipid and blood glucose levels in patients with destructive periodontal disease

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Abstract

Hyperlipidaemia and hyperglycaemia are major risk factors for cardiovascular disease. In recent years, some evidence has been presented that periodontal disease is associated with an increased risk of cardiovascular disease. To further elucidate this association, we have studied standard blood chemistry variables known as risk markers for cardiovascular disease in periodontally diseased and healthy subjects. We have measured levels of plasma lipids and fasting blood glucose in 39 subjects with moderate periodontal disease (age 50–60 years) and compared the results with those obtained in 40 age- and sex-matched controls. Both groups were systemically healthy according to their medical history. Total cholesterol, low density lipoprotein cholesterol and triglycerides were significantly higher in periodontally diseased subjects by about 8% ($p<0.03$), 13% ($p<0.003$) and 39% ($p<0.001$), respectively, when compared to controls. Although subjects with diabetes were excluded from the study, we found significantly higher blood glucose levels in the patient than in the control group (85±25 versus 73±17 mg/dl; $p<0.02$). There was also a significantly higher frequency of pathological plasma lipid profiles in the patient than in the control group. The results indicate that hyperlipaemia and pre-diabetes may be associated with periodontal disease in systemically healthy subjects. These data do not allow us to decide, whether periodontal disease causes an increase in hyperlipaemia and in a prediabetic state or whether periodontal disease and cardiovascular disease share hyperlipidaemia and the prediabetic state as common risk factors.

Key words: periodontitis; cardiovascular disease; plasma lipids; blood glucose; risk factors

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Periodontal disease is an infectious disease caused by a small group of predominantly anaerobic gram-negative bacteria present on the tooth surface as biofilms. Lipopolysaccharides and other microbial substances gain access to the gingival tissues, initiate and perpetuate inflammation, resulting in production of high levels of proinflammatory cytokines, which lead to the destruction of the periodontal ligament and alveolar bone.

Several studies have indicated that subjects with periodontal disease may have a higher risk for cardiovascular diseases when compared to subjects with a healthy periodontium (Mattila et al. 1989, Syrjänen et 1989, Paunio et al. 1993, DeStefano et al. 1993, Grau et al. 1997, Beck et al. 1998, Joshipura et al. 1998, Kinane 1998, Loesche & Lopatin 1998). So far, the causality and possible pathways of the association between periodontal disease and cardiovascular disease are obscure. Factors that place individuals at risk for periodontitis may also place them at risk for cardiovascular disease; that means that periodontitis and cardiovascular disease may share common risk factors, such as smoking, diabetes, behavioural factors, ageing, male gender. In a number of case-control or cohort studies, even after adjusting for these factors in multivariate analysis, the association remained statistically significant (DeStefano et al. 1993, Joshipura et al. 1996, Beck et al. 1998). Thus, one can speculate that periodontal disease as a chronic infection may be related with cardiovascular disease through infection related mediators and hyperactivity

of white blood cells and of blood platelets, thus promoting the development of atherosclerosis (Valtonen 1991, Loesche 1995, Offenbacher 1996, Ellis 1997, Beck et al. 1998, Herzberg & Meyer 1998).

Hypercholesterolaemia, in particular increased plasma levels of low density lipoprotein (LDL) cholesterol, hypertriglyceridaemia and diabetes mellitus are major risk factors of cardiovascular disease. In contrast, increased levels of high density lipoprotein (HDL) cholesterol have been shown to be associated with a low risk of cardiovascular disease (Schaefer et al. 1995, Barter & Rye 1996, Grundy 1998). Recently, we could demonstrate that subjects with hypercholesterolaemia and cardiovascular disease have a significantly worse periodontal condition than community based control subjects. Furthermore, the degree of periodontal breakdown was positively correlated to plasma cholesterol levels (Pohl et al. 1995).

In the present study, we measured fasting plasma lipids as well as blood glucose in non-diabetic periodontal diseased patients and control subjects.

Material and Methods

Subjects

39 subjects with periodontitis (20 female and 19 male, age 50 to 60 years, mean 54.8±3.1) and 40 control subjects (25 female and 14 male, ages 50 to 60 years, mean 55.4±2.8) participated in this study. Both patients and controls were sequentially recruited within 6 months from subjects who went to the private dentist for annual routine oral examination. After being informed on the purpose of the study, the patients signed informed consent forms. The study protocol was approved by the local ethical committee. Both periodontitis and control subjects were asked to answer a questionnaire with regard to their social and general medical status. If doubts about the medical status occurred their physician was consulted. Exclusion criteria were any dental treatment during the past 6 months, diabetes mellitus or any other endocrine disease, myocardial infarction, stroke and cancer. Smokers (one control and 7 patients) were also excluded from the study. No subject took any drug against hypercholesterolaemia. All subjects with more than 3 pockets with a probing depth ⩾4 mm were included in the group of periodontitis subjects.

Dental variables

All subjects were examined by the same dentist. All dental variables were assessed at 6 different sites around each tooth.

- *Percentage of plaque:* The presence or absence of plaque was registered qualitatively.
- *Bleeding on probing:* If bleeding occurred immediately after probing for pocket depth it was reported as positive.
- *Probing pocket depth* was measured with a standard periodontal probe (Ainamo et al. 1982) within 1 mm limits. Pockets were categorised in healthy (depth up to 3 mm), moderated diseased (4 and 5 mm) and advanced diseased (≥ 6mm) and are reported as mean percentage.
- *Number of missing teeth* excluding wisdom teeth.

Measurements of serum lipids and blood glucose

After enrolling into the study periodontitis as well as control subjects were asked to consult their family doctor for measuring fasting plasma lipid and blood glucose concentrations. The measurements were done in the same local laboratory of clinical chemistry using routine enzymatic methods. To identify subjects with pathological values the following cut-off points were used according to the laboratory's recommendation: total cholesterol >230 mg/dl, LDL-cholesterol >160 mg/dl, HDL-cholesterol <45 mg/dl, triglycerides >200 mg/dl, blood glucose >120 mg/dl. These values are applicable to individual with a normal risk for cardiovascular disease (Wood 1998).

Statistical analysis

All dental data were expressed on a patient basis. Data are presented as mean and standard deviation. Differences between means were proved for significance using the Student's *t*-test for unpaired samples. Because of multiple tests of the probing depth categories a Bonferroni adjustment was performed. After categorising the blood chemistry values in normal and diseased categories, differences in frequencies were tested for significance using Chi-quadrate test (Statview 5.0, SAS Inc.).

Results

According to the questionnaire, there were no differences in the social status of periodontitis and control subjects. According to the extent of pocketing, most of the patients suffered from moderate periodontitis; 47.2±24.6% of sites had a probing depth of 4–5 mm and 8.6±16.3% of sites had a probing depth of more than 5 mm. In controls few moderate deep pockets (8.7±8.5% of sites), but no deep pockets were present. As to expect, bleeding on probing was more frequent in the periodontally diseased subjects (25.1±26.3%) than in the control subjects (5.0±6.9%, p=0.0001). Control subjects had significantly fewer missing teeth than the periodontitis patients (7.9±5.7 versus 11.2±7.4, p= 0.03). A qualitative estimate of plaque accumulation did not reveal a significant difference between periodontitis patients and control subjects (50±19% versus 48±23%).

As shown in Table 1, mean plasma cholesterol and LDL cholesterol levels in periodontitis subjects were significantly higher by about 8% and 13% as compared to controls. Also plasma triglyceride levels were higher in patient than in control subjects (+39%), but no difference was seen in HDL cholesterol. Highly significant differences between periodontitis and control subjects were also observed when the frequency of pathological plasma lipid levels were estimated. The frequency of hyperchol-

Table 1. Blood lipid and glucose levels (mg/dl; mean and standard deviation) in controls and periodontitis patients

	Controls		Patients		
	mean	sd	mean	sd	p-value
total cholesterol (mg/dl)	224.8	39.1	243.6	37.3	0.03
LDL cholesterol (mg/dl)	165.5	35.9	187.3	37.3	0.01
HDL cholesterol (mg/dl)	55.8	17.8	52.2	11.7	n.s.
triglycerides (mg/dl)	126.2	53.1	175.6	115.5	0.02
glucose (mg/dl)	73.3	16.5	84.5	24.5	0.02

HDL=high density lipoprotein, LDL=low density lipoprotein, n.s.=not significant.

Table 2. Frequency of pathological values of plasma lipids and blood glucose levels in controls and periodontitis patients; cut-off values (mg/dl) are reported in parenthesis

		Controls		Patients		
Cutt off	(mg/dl)	under	beyond	under	beyond	*p*-value
total cholesterol	(>230)	25	15	15	24	0.03
LDL cholesterol	(>160)	22	18	9	30	0.003
HDL cholesterol	(<45)	10	30	11	28	n.s.
triglycerides	(>200)	38	2	26	13	0.001
glucose	(>120)	40	0	39	0	n.s.

esterolaemia in patients was about twice of that in controls. This was true for total cholesterol as well as LDL cholesterol. Pathological triglyceride levels were about 6.5 times more frequent in periodontitis subjects when compared to controls, whereas no difference was seen in HDL cholesterol (Table 2).

Although diabetes mellitus was one of the exclusion criteria in our study, we also determined fasting blood glucose levels. Indeed we did not observe pathological values in periodontitis or control group (Table 2). However, there was a significant difference in the mean values of both groups. Mean blood glucose was about 15% higher in patients when compared to controls (Table 1).

Discussion

It is well-established that marginal periodontitis and cardiovascular disease share some common risk factors, such as diabetes mellitus, smoking, poor health care habits (DeStefano et al. 1993, Pohl et al. 1995, Papapanou 1996, Beck et al. 1998). The social background of both groups was balanced, and smokers were excluded from the study. Although patients with known diabetes mellitus were also excluded from our study, values of fasting blood glucose levels in periodontitis patients were slightly but significantly higher than in patients. This observation may indicate that these patients have some problems with their glycaemic control and are in a pre-diabetic condition. Poor glycaemic control is known as an established risk factor of periodontitis (Nishimura et al. 1998, Lalla et al. 1998). However there is also some evidence that severe periodontal disease may deteriorate glycaemic control (Taylor et al. 1996, Grossi et al. 1997, Grossi & Genco 1998). It is discussed that some cytokines, such as TNFα, IL-1β or interferon γ, that are produced in response to an infection with gram-negative bacteria may be responsible for an insulin resistance and subsequent poor glycaemic control in periodontitis patients (Liu et al. 1998, Reimers 1998, Shiba et al. 1998).

Compared to controls, subjects with periodontitis had higher plasma levels of total cholesterol, LDL cholesterol and triglycerides, and the frequency of pathological lipid profiles was more prevalent in patients than in controls. Periodontal disease is a microbial infection caused by gram-negative bacteria. Acute infections are known to interfere with lipid metabolism, and elevation of plasma triglycerides has been observed especially in infection with gram-negative bacteria (Alvarez et al. 1986, Wanner et al. 1997). These changes are thought to be mediated by cytokines, which may be produced at the inflamed periodontal tissue in high quantities (Grunfeld et al. 1989, Valtonen 1991, Beck et al. 1998). Infections with *Chlamydia pneumonia* and with *Helicobacter pylori* which are believed to be associated with an increased risk of cardiovascular disease has been recently shown to be associated with increased plasma cholesterol and triglyceride levels (Ellis 1997, Laurila et al. 1997, 1999). These findings support the hypothesis that chronic infections including periodontitis may modify the serum lipid profile in a way that increases the risk of atherosclerosis.

A possible role of hyperlipaemia for periodontitis is also obvious from several studies. Hyperlipaemia is known to cause a hyperactivity of white blood cells (Croft et al. 1990, Krause et al. 1993). Hyperactivity of white cells, e.g., increased production of oxygen radicals, have been shown to be frequently associated with progressive periodontitis in adults (Krause et al. 1990, Shapira et al 1991, Gustafson & Asman 1996). In animals feeding a cholesterol-rich diet has been demonstrated to produce periodontitis (Ueno 1969).

The pro-atherogenic changes in plasma lipids and blood glucose that were observed in our periodontitis patients may provide some further evidence for the close association between periodontitis and cardiovascular disease. However, it is not clear yet whether the observed changes in lipid and glucose metabolism are the cause or the consequence of periodontitis. Further studies are needed to find out the mechanisms underlying the association between periodontitis and cardiovascular disease.

Zusammenfassung

Plasmalipid- und Blutglukosespiegel bei Patienten mit destruktiver Parodontalerkrankung

Hyperlipidämie und Hyperglykämie sind wesentliche Risikofaktoren für kardiovaskuläre Erkrankungen. In den letzten Jahren wurde von verschiedenen Autoren darüber berichtet, daß Parodontalerkrankung mit einem höheren Risiko für kardioivaskuläre Erkrankungen assoziiert ist. Um weitere Hinweise für eine solche Assoziation zu erhalten, haben wir Standardblutvariable, die als Risikofaktoren für kardiovaskuläre Erkrankungen bekannt sind, bei parodontal erkrankten und gesunden Personen untersucht. Wir haben die Spiegel der Plasmalipide und der Nüchternblutglukose bei 39 Patienten mit moderater Parodontalerkrankung gemessen (Alter 50–60 Jahre) und mit den Werten von 40 alters- und geschlechtsentsprechenden Kontrollpersonen verglichen. Beide Gruppen waren nach der Anamnese systemisch gesund. Gesamt- und LDL-Cholesterol sowie Triglyceride waren bei den parodontal Erkrankten um etwa 8% ($p<0.03$), 13% ($p<0.003$) und 30% ($p<0.001$) signifikant höher als bei den Kontrollen. Obwohl Personen mit Diabetes von den Studie ausgeschlossen wurden, fanden wir signifikant höhere Blutglukosewerte bei den Patienten als bei den Kontrollen (85 ± 25 versus 73 ± 17 mg/dl; $p<0.02$). Pathologische Plasmalipidwerte wurden bei den Patienten signifikant häufiger als bei den Kontrollen beobachtet. Die Ergebnisse zeigen, daß Hyperlipidämie und Prädiabetes bei systemisch gesunden Personen mit Parodontalerkrankung assoziiert sein können. Diese Daten erlauben aber nicht zu entscheiden, ob die Parodontalerkrankung eine Hyperlipidämie oder einen prädiabetischen Zustand verursachen oder ob die Parodontalerkrankung und kardiovaskuläre Erkrankungen Hyperlipidämie und prädiabetischen Status als gemeinsame Risikofaktoren haben.

Résumé

Niveaux des lipides plasmatiques et du glucose sanguin chez les patients avec maladie parodontale destructice

L'hyperlipidémie et l'hyperglycémie sont des facteurs de risque très importants pour les maladies cardio-vasculaires. Au cours des demières années des données indiquant une association de la maladie parodontale avec un

risque accru de maladies cardio-vasculaires ont été présentées. Pour mettre cette association ultérieurement en lumière, nous avons étudié chez des patients avec maladie parodontale et chez des patients sains des variables standard de chimie du sang, connues comme marqueurs de risque de maladie cardio-vasculaire. Nous avons mesuré le niveau des lipides plasmatiques et du glucose sanguin à jeun chez 39 sujets atteints de maladie parodontale modérée (âgés de 50–60 ans) et comparé les résultats avec ceux qu'on on obtenait chez 40 sujets témoins (control) d'âges et de sexes correspondants. L'anamnèse médicale indiquait que la santé systémique était bonne dans les deux groupes. Le cholestérol total, le cholestérol lié aux lipoprotéines de faible densité et les triglycérides étaient significativement plus élevés chez les sujets avec maladie parodontale que chez les témoins, respectivement d'environ 8% ($p<0.03$), 13% ($p<0.003$) et 39% ($p<0.001$). Bien que les sujets diabétiques aient été exclus de cette étude, nous avons trouvé des niveaux de glucose sanguin significativement plus élevés chez les patients que dans le groupe témoin (85 ± 25 versus 73–17 mg/dl; $p<0.02$). On trouvait aussi chez les patients une fréquence significativement plus élevée des profils pathologiques de lipides plasmatiques que dans le groupe témoin. Ces résultats indiquent qu'une hyperlipémie et un état prédiabétique peuvent être associés avec une maladie parodontale chez des sujets en bonne santé systémique. Ces données ne nous permettent pas de décider si la maladie parodontale cause une augmentation de l'hyperlipémie et de l'état prédiabétique, ou si maladie parodontale et maladie cardio-vasculaire ont en commun l'hyperlipidémie et l'état prédiabétique comme facteurs de risque.

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