

Metabolic disorders related to obesity and periodontal disease

TOSHIYUKI SAITO & YOSHIHIRO SHIMAZAKI

Being overweight and obese are important risk factors for various adult diseases, including type 2 diabetes, hyperlipemia, hypertension, cholelithiasis, arteriosclerosis, and cardiovascular and cerebrovascular disease (31). Type 2 diabetes is rapidly becoming prevalent in Japan and the U.S.A. and is much more common in the obese. Cardiovascular disease is the most common cause of death and accounts for more than 17 million deaths annually. The World Health Organization (WHO) estimated that 1 billion people were overweight [body mass index (BMI) > 25] or obese (BMI > 30) in 2005 and the number will increase to 1.5 billion by 2015 if current trends continue (85). Although obesity was once considered a health problem only in wealthy countries, the WHO now states that obesity is rising dramatically in poor and intermediate countries. This is the result of a number of lifestyle-related factors, including a global shift in diet towards increased energy, fat, and sugar intake, and a trend towards decreased physical activity because of the sedentary nature of modern work and transportation.

Recently, obesity has emerged as one of the risk indicators of periodontal disease (Fig. 1A) and conversely, the remote effects of periodontal disease on various systemic diseases have been proposed (Fig. 2). Among the systemic health disorders shown in Fig. 2, type 2 diabetes and cardiovascular disease are established obesity-related diseases (25, 31, 45, 67). If obesity is a true risk factor for periodontal disease, the association among periodontal disease, obesity, and type 2 diabetes or cardiovascular disease must be very complex because each is a confounding factor for the other. In addition, several studies have suggested that periodontal disease affects both glucose and lipid metabolisms, which are themselves very important factors in the development of both type 2 diabetes and cardiovascular disease. Considering these issues, the knowledge from various recent reports must be consolidated. The first part of this

document reviews the relationship between obesity and periodontal disease. Then, it reviews and discusses reports on the influence of periodontal disease on obesity-related metabolic disorders, such as glucose and lipid metabolism, which cause glucose intolerance and dyslipidemia.

Obesity and periodontal disease

The first paper on the relationship between obesity and periodontal disease (Table 1) was published in 1977, and showed that obese-hypertensive rats are more likely to have periodontal tissue deterioration than normal rats (50). In humans, it was reported that obese Japanese subjects were more likely to have periodontal disease than thin people in 1998 (54). A higher BMI was related to a greater prevalence of periodontal disease in 241 apparently healthy adults aged 20–59 years using BMI and body fat to assess obesity and the community periodontal index (CPI) for periodontal status. A multivariate analysis adjusted for age, sex, oral hygiene, and smoking found an 8.6 times higher odds ratio of periodontal disease for subjects with a BMI \geq 30 compared to subjects with a BMI < 20. Body fat was analyzed using dual-energy X-ray absorptiometry and a 5% increase in body fat corresponded to a 30% increased risk of periodontal disease. In that study, neither glycosylated hemoglobin values (3.4–6.3%) nor the fasting blood glucose concentration (73–131 mg/dl) were correlated with the incidence of periodontal disease, which was probably because those ranges were within normal limits or borderline.

In contrast, periodontal disease was more prevalent in the subjects with a serum high-density lipoprotein cholesterol concentration <60 mg/dl, suggesting that periodontal disease is exacerbated by some conditions associated with obesity, such as 'the metabolic syndrome' (13, 78), a clustering of

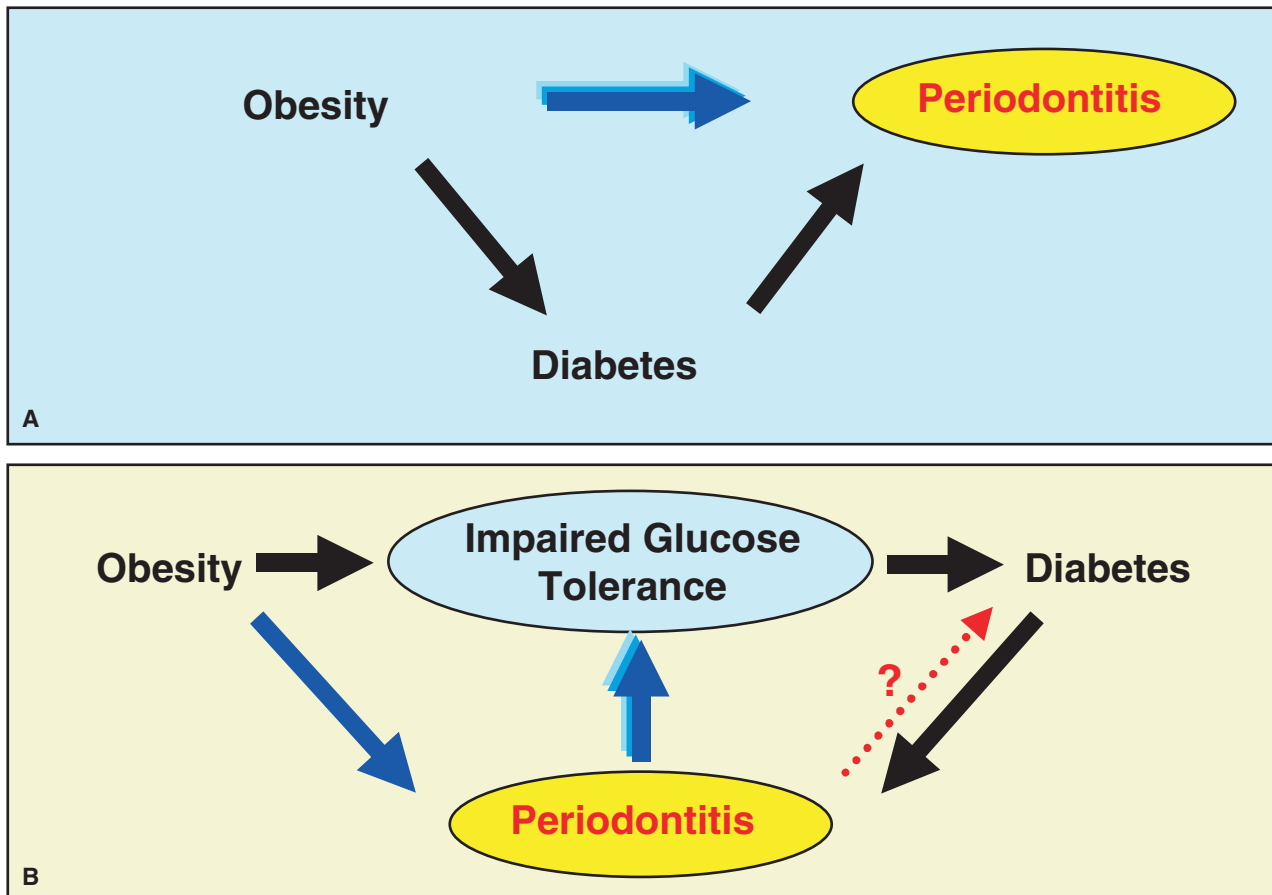


Fig. 1. (A,B) Relationships among obesity, diabetes, and periodontal disease. The black arrows indicate established relationships. Blue arrows indicate associations from recent reports.

dyslipidemia and insulin resistance. Buhlin et al. (7) also reported that a high BMI (>26 in men and >25 in women) and cholesterol were significantly associated with severe periodontitis in a multivariate model of a case-control study. A relationship between periodontal disease and exercise capacity, which is closely associated with obesity, has been reported (42, 55). Of the various physical strength tests, the maximum oxygen uptake (VO_{2max}), which is closely related to daily exercise, was significantly associated with periodontal disease, supporting the relationship between obesity and periodontal disease from the perspective of physical strength (55). Merchant et al. (42) also reported that increased physical activity decreased periodontal risk in men. In their study, 'metabolic equivalents' (39) were calculated from the energy costs for each activity based on answers to a questionnaire. An additional adjustment for BMI attenuated the odds ratio for periodontitis and in a subgroup analysis with a BMI ≥ 25 a more significant relationship was found between physical activity and periodontitis (42).

Of the different types of obesity, upper body obesity, which is related to visceral fat accumula-

tion, increases the risk of various adult diseases, especially type 2 diabetes (5) and cardiovascular disease (45). Upper body obesity was also reported to have a significant relationship with periodontal disease in 643 Japanese subjects (56). In that study, BMI, body fat determined using dual-energy X-ray absorptiometry, and the waist-to-hip ratio were used as indices of obesity and all these indices were connected to periodontal disease using the CPI criteria. The subjects were then divided into two groups using a waist-to-hip ratio ≥ 0.8 for women and ≥ 0.9 for men as the criterion for upper body obesity. Then, both groups were divided into four BMI categories. Multivariate analysis using known risk factors of periodontal disease showed a significant relationship between BMI and periodontal disease only in the subjects with high waist-to-hip ratios. Similar results were obtained using body fat instead of BMI. These findings suggest that visceral fat accumulation in upper body obesity is associated with periodontal disease.

Several studies have been published using data from the third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional

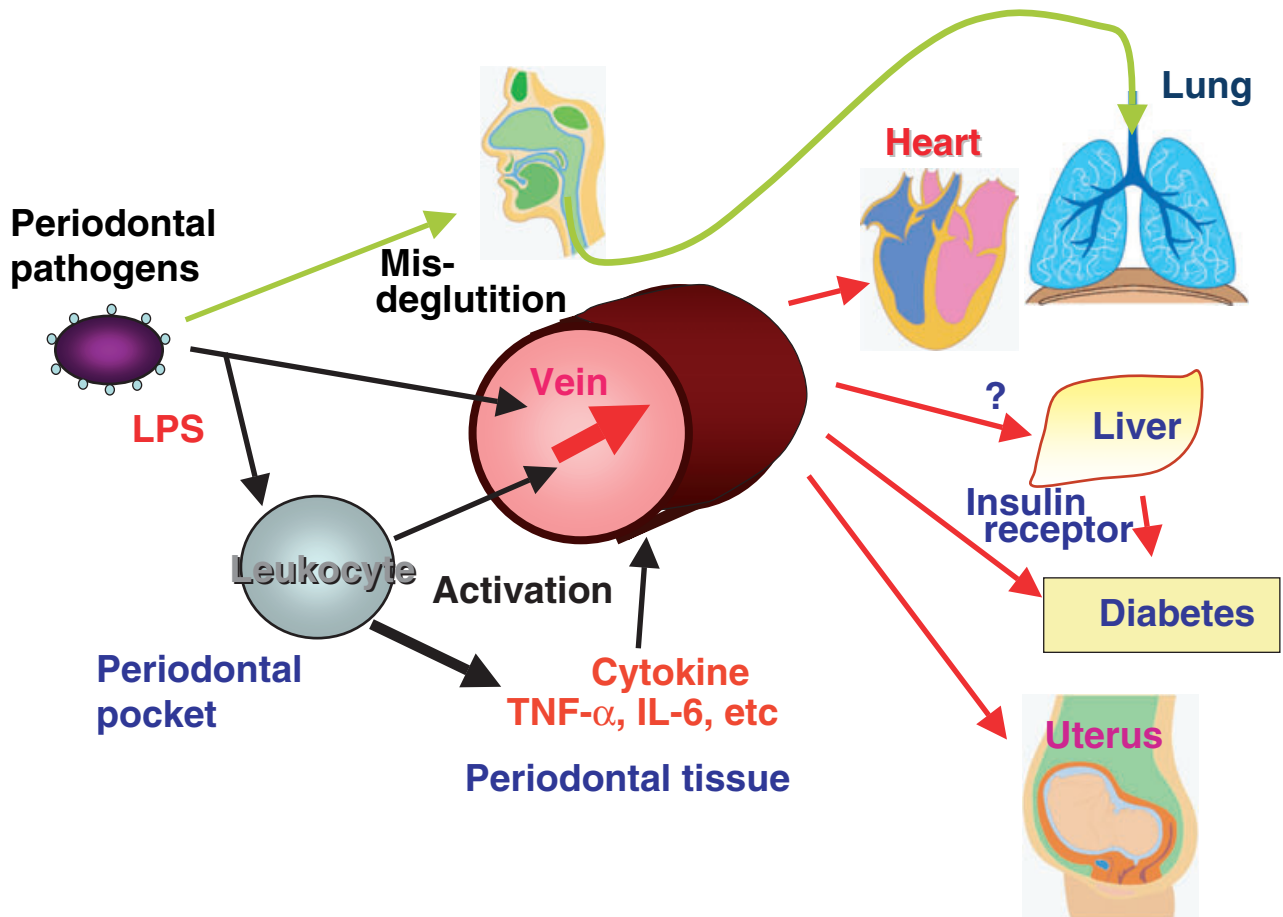


Fig. 2. Remote effects of periodontal disease on systemic health. LPS, lipopolysaccharide; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6.

national survey conducted by the National Center for Health Statistics (NCHS) from 1988 to 1994. This sample is considered to be representative of U.S. citizens. Using NHANES III subjects, Woods et al. (84) reported that BMI and the waist-to-hip ratio were associated with various periodontal indices, such as attachment loss, pocket depth, gingival bleeding, and calculus index, but fat-free mass was not after adjustment. Interestingly, they showed that these associations were not linear. Also using NHANES III, Al-Zahrani et al. (1) reported that BMI and waist circumference were associated with periodontal disease (for both attachment loss ≥ 3 mm and probing depth ≥ 4 mm) especially in the subset of young adults aged 18–34 years. This was significant in all subjects of all age groups; however, no significant association was found between obesity and periodontal disease when the middle and older age groups were analyzed separately. One reason may have been that several affected teeth had been extracted in aged subjects and many of the remaining teeth were healthier, making it difficult to detect the relationship between obesity and periodontal disease. Indeed, a

national survey held in Japan showed that the prevalence of periodontal disease decreased after 50 years of age because of an insufficient number of teeth to examine. Various reports found a stronger association between obesity and cardiovascular and chronic adult diseases in younger age groups (16, 44, 67, 79). Aging is associated with an increase in body fat mass (26, 70) and this means that some older obese subjects gain weight as part of the aging process. The association between obesity and periodontal disease could be more pronounced among younger than older adults because of the confounding metabolic changes in later life. Using the same subjects, it was reported that three health-enhancing behaviors were associated with a lower prevalence of periodontitis: maintaining a normal weight (BMI 18.5–24.9), engaging in exercise, and eating a high-quality diet (2). A case-control study showed that alveolar bone loss is related to obesity (BMI ≥ 30) before the age of 40, but not at ages ≥ 40 years (3). A study in Thailand found that BMI was not associated with attachment loss in 2005 subjects aged between 50 and 73 years (73). This concurs with the two

Table 1. Studies on the relationship between obesity and periodontal disease

| Authors | Study design | Subjects | Criteria for periodontitis | Major results |
|---------------------------|-----------------|--|---|---|
| Perlstein & Bissada (50) | Animal model | 44 Rats | Histopathological evaluation | Obese-hypertensive rats showed the most severe periodontal destruction |
| Saito et al. (54) | Cross-sectional | Convenience N = 241 (172 females, 69 males) 20–59 years | Max. probing depth ≥ 4 mm (CPI) | BMI and body fat were associated with periodontitis |
| Saito et al. (55) | Cross-sectional | Convenience N = 241 (172 females, 69 males) 20–59 years | Max. probing depth ≥ 4 mm (CPI) | VO _{2max} was associated with periodontitis |
| Nishimura et al. (47) | Case-series | Convenience N = 79 Subjects with NIDDM | Max. probing depth ≥ 4 mm (CPI) | BMI was associated with periodontitis in NIDDM patients |
| Saito et al. (56) | Cross-sectional | Convenience N = 643 (512 females, 131 males) 19–79 years | Max. probing depth ≥ 4 mm (CPI) | WHR, BMI, and body fat were associated with periodontitis |
| Wood et al. (84) | Cross-sectional | NHANES III N = 8842 | Percent sites with attachment loss ≥ 3 mm | WHR and BMI were associated with attachment loss nonlinearly |
| Al-Zahrani et al. (1) | Cross-sectional | NHANES III N = 13665 18–90 years | Attachment loss ≥ 3 mm and probing depth ≥ 4 mm | BMI ≥ 30 and high waist were associated with periodontitis, especially in younger adults (18–34 years) |
| Buhlin et al. (7) | Case-control | N = 96 50 periodontitis and 46 periodontally healthy subjects, 36–70 years | Seven or more sites with ≥ 6 mm of attachment loss | BMI > 26 in men and > 25 in women was associated with periodontitis |
| Torrungruang et al. (73) | Cross-sectional | N = 2005 50–73 years | Mean attachment loss | BMI and waist were not associated with periodontitis |
| Alabdulkarim et al. (3) | Case-control | N = 400 200 obese (BMI ≥ 30) 200 non-obese (BMI < 25), ≥ 18 years | Alveolar bone score <60 | Obesity (BMI ≥ 30) was associated with alveolar bone loss, especially in young adults (<40 years) |
| Saito et al. (58) | Cross-sectional | Community Women, N = 584, 40–79 years | Upper 20th percentile of mean probing depth and mean attachment loss | BMI, body fat, and WHR were associated with deep pockets, adjusted for OGTT |
| Nishida et al. (46) | Cross-sectional | Convenience N = 372, 20–59 years | Upper 20th percentile of % probing depth ≥ 3.5 mm | BMI > 26 was associated with periodontitis |
| Socransky & Haffajee (65) | Case-control | N = 415 329 periodontitis and 86 periodontally healthy subjects | Probing depth, attachment loss, bleeding on probing, subgingival plaque | The proportion of <i>T. forsythia</i> was increased in BMI > 35 |

NIDDM, non-insulin-dependent diabetes mellitus; CPI, community periodontal index; BMI, body-mass index; WHR, waist-to-hip ratio; OGTT, oral glucose tolerance test; VO_{2max}, maximum oxygen uptake.

studies mentioned above, which found that obesity was not associated with periodontal disease in subjects ≥ 35 or > 40 years of age (1, 3).

Several confounders between obesity and periodontal disease can be imagined. A BMI > 25 is associated with dental health behavior, including the frequency of dental checkups, frequency of tooth-brushing, and the consumption of sweet foods or beverages, as well as with general health behavior (87). These factors easily remind us of the development of periodontal disease, although these factors, especially tooth-brushing and the amount of dental plaque accumulation, have been considered confounding factors and adjusted for in many studies. Nishida et al. (46) examined the association between periodontal disease and several lifestyle-related factors, including smoking, alcohol consumption, and obesity, and showed that smoking had the strongest association, followed by obesity, using the classification and regression tree method. The criterion used for periodontitis in this study was the upper 20th percentile of the subjects with pockets deeper than 3.5 mm. A community-based study of women showed that deep pockets were significantly associated with obesity, after adjusting for glucose tolerance using a fasting 75-g oral glucose tolerance test (58), which constitutes the definitive method for assessing a patient's glucose tolerance as defined by the Japan Diabetes Society (33), American Diabetes Association, and WHO (4). Although oral glucose tolerance test results were closely associated with both periodontal condition and obesity, the relationship between the obesity indices and deep pockets was more significant than that between the oral glucose tolerance test results and deep pockets. The latter was not significant in multivariate models, suggesting that the obese condition is associated with periodontal disease independent of deteriorated glucose condition. The association between obesity and attachment loss was weaker than that with pocket depth (58). Nishimura et al. (47) reported a relationship between BMI and periodontal disease in type 2 diabetes mellitus patients. From these studies, obesity may be associated with periodontal disease independent of diabetes, as shown in Fig. 1A. In ongoing case-control studies at The Forsyth Institute in the U.S.A. (65), obesity was related to deep pockets, attachment loss, bleeding on probing, and plaque accumulation and an increase in the proportion of *Tannerella forsythia* (*Bacteroides forsythus*) was marked in extremely obese subjects with a BMI > 35 . The bacterial flora in dental plaque may differ in obese subjects.

Obesity and dental caries

Some studies have examined the relationship between obesity and dental caries in children and adolescents. Tuomi (75) studied obesity as a predictor of caries increment in children. In that study, obesity alone could not predict dental decay, while the combined use of obesity and earlier caries experience was a more sensitive predictor of further caries than the use of early caries experience alone. Willershausen et al. (82) examined the relationship between weight and frequency of caries in elementary school children in Germany, and showed that the subjects with normal weights had significantly fewer dental caries, in both their primary and permanent teeth, than the overweight children. Larsson et al. (35) examined 15-year-olds, and reported that adolescents with a high level of dental caries had more risk factors for cardiovascular disease, including a higher BMI, than caries-free adolescents. A significant positive correlation was found between the decayed-filled surface-score and BMI in a multiple linear regression analysis. Larsson et al. (34) previously reported that eating a nutritionally poorer diet was associated with a high dental caries score in adolescents, suggesting that poorer eating habits at younger ages could lead to cardiovascular disease later in life. Recently, Tomofuji et al. (71) reported that a high-cholesterol diet was associated with the proliferation of junctional epithelium with increasing bone resorption in rat periodontitis. This could explain the relationship between obesity and periodontal disease, because a high-cholesterol diet leads to obesity. As both oral health and obesity are closely associated with daily diet, dietary counseling for children and adolescents concerning oral health problems, including dental caries and periodontal disease, and obesity may reduce the risk of oral diseases, as well as the risk of developing cardiovascular disease in later life. Malnutrition and poor eating habits, related to both oral health and cardiovascular disease, may strengthen the relationship between oral health and cardiovascular disease.

Obesity and the number of teeth

Several studies have indicated that a high BMI is associated with a decreased number of teeth or edentulousness in middle-aged women (17). It has been reported that obesity is associated with dental

caries in adolescents (35), which could be a reason for fewer teeth. Periodontal disease worsened by obesity in younger adults could be another reason for tooth loss in later life.

Conversely, it has been reported that edentulousness was a significant risk factor for a 10% weight loss over 1 year among community-dwelling older adults (53). Severe periodontal disease was also reported to be a risk factor for weight loss in older adults (81). The number of sites with a probing depth ≥ 6 mm was causally related to a 5% weight loss over 2 years in 1053 community-dwelling elderly aged 65 years and over. These factors may help explain why the relationship between obesity and periodontal disease is not dramatic in the elderly.

The mechanism connecting obesity and periodontal disease

There are few reports on the mechanism connecting obesity and periodontal disease. Conversely, a huge number of studies have reported on obesity as a medical problem. From these papers, several ways in which obesity affects periodontal tissue directly can be proposed. Obesity affects host immunity (40, 66, 69). It has been reported that obese-hypertensive rats are more likely to have periodontitis than normal rats and that the periodontal blood vessels of these rats show intimal thickening, indicating diminished blood flow (50). A high-cholesterol diet has been associated with the proliferation of junctional epithelium, with increasing bone resorption in rat periodontitis (71). As a high-cholesterol diet leads to fat accumulation directly, an elevated serum cholesterol level may be a reason for the relationship between obesity and periodontal disease.

Upper body obesity, i.e. abdominal adiposity, has greater adverse effects on health than lower body obesity (52, 78). Visceral fat accumulation, which is frequently observed in upper body obesity, increases the risk of cardiovascular disease (45) and type 2 diabetes (5). An increase in visceral fat is associated with insulin resistance and increased liver fat (5, 20). An increase in the waist-to-hip ratio is reported to be a predictor of hepatic steatosis independent of BMI (20, 32). One study showed a significant association between periodontitis and serum aspartate aminotransferase, alanine aminotransferase, and cholinesterase levels and the aspartate aminotransferase-to-alanine aminotransferase ratio, suggesting that subjects with periodontitis also tend to have hepatic steatosis (59). Visceral fat, which leads to

hepatic steatosis, may also increase the risk of periodontitis.

Recent studies have indicated that adipose tissue, especially visceral adipose tissue, is an important organ that secretes several bioactive substances known as adipocytokines, which include tumor necrosis factor- α , as shown in Fig. 3 (63, 64). These may affect periodontal tissue directly. Tumor necrosis factor- α mediates endotoxin-induced injury in various organs, including periodontal tissue (19). As tumor necrosis factor- α is secreted from adipose tissue, it may enhance periodontal degradation. A recent study of young adults showed that tumor necrosis factor- α in gingival crevicular fluid is correlated with BMI in subjects with a BMI ≥ 40 (38). The level of tumor necrosis factor- α in gingival crevicular fluid was positively associated with BMI in subjects without periodontal disease, suggesting that tumor necrosis factor- α in gingival crevicular fluid is derived from adipose tissue in obese subjects, which concurs with the finding that obesity is a type of low-grade systemic inflammatory disease. This suggests that tumor necrosis factor- α from adipose tissue in young adults will cause deterioration of their periodontal tissue in later life, although they do not have periodontal disease when they are young. Plasminogen activator inhibitor-1, which is strongly expressed in visceral fat (63), induces the agglutination of blood and raises the risk of ischemic vascular disease. Therefore, plasminogen activator inhibitor-1 may also decrease blood flow in the periodontium of obese subjects to promote the development of periodontal disease. Indeed, the plasminogen-activating system was reported to play an important role in gingival inflammation (30).

Leptin is the best-known substance secreted from adipose tissue. Leptin stimulates the immune system as it enhances cytokine production and phagocytosis by macrophages (18). A strong negative relationship between the plasma levels of leptin and interleukin-6 has been reported in sepsis (72). Most recently, leptin was found to act in bone formation (8, 80). It has been reported that leptin is present within healthy and marginally inflamed gingiva and decreases in concentration as the adjacent probing depth increases (28). Thus, leptin may play an important role in the development of periodontitis.

Diabetes and periodontal disease

As mentioned previously, obesity is the most important risk factor for type 2 diabetes, and both

Development of glucose intolerance in the past 10 years

○ 406 subjects with NGT in 1988 → ○ 72 subjects developed IGT until 1998

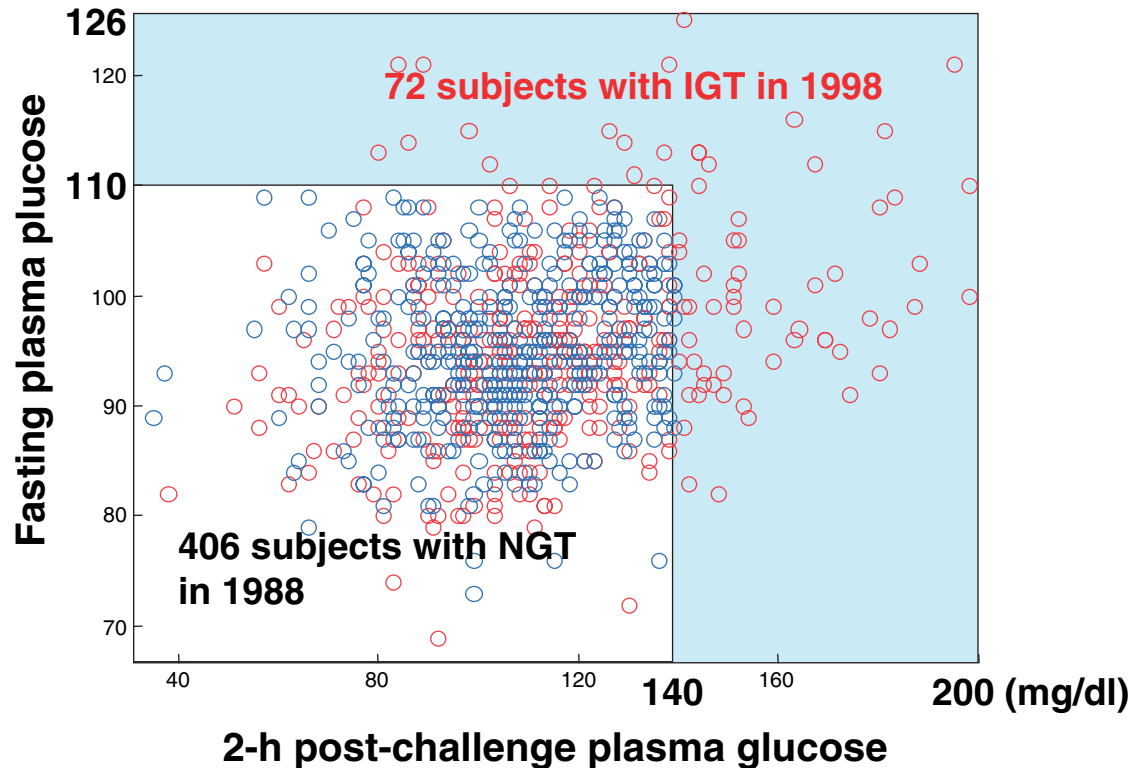


Fig. 4. Results of 75-g oral glucose tolerance tests conducted in Hisayama in 1988 and 1998 for the same subjects. Blue circles indicate subjects with a normal glucose tolerance (NGT) in 1988, which dispersed into red circles in 1998. In 72 subjects, the glucose condition had deteri-

orated over the 10 years. Impaired fasting glucose (IFG) was included in impaired glucose tolerance (IGT) in this study. Nine diabetic subjects in 1998 were eliminated. Unpublished data from reference (57).

higher tertiles of alveolar bone loss ($P = 0.03$ for trend). In the subjects with the highest tertile of alveolar bone loss, the adjusted odds ratio for impaired glucose tolerance to normal glucose tolerance was 4.27 (95% CI, 1.41–12.9; $P = 0.01$). Although diabetes has been reported to have an adverse effect on the health of periodontal tissues, the effect of impaired glucose tolerance has not been reported. Several studies on the relationship between diabetes and periodontal disease found an insignificant association of impaired glucose tolerance as a risk indicator of periodontal disease (12, 48, 58, 74). At present, we propose the scheme shown in Fig. 1B, which was modified from Fig. 1A with the inclusion of impaired glucose tolerance between obesity and diabetes. A prospective cohort study is required to clarify whether periodontal disease affects glucose tolerance or impaired glucose tolerance affects periodontal disease.

Dyslipidemia and periodontal disease

Nutrition influences immune function (40). Since the cell membrane is composed primarily of phospholipids, its makeup is influenced by the type and quantity of lipids ingested. This is also the case for immunocytes, such as polymorphonuclear leukocytes. Indeed, it has been reported that hyper-lipid food or fatty acids depress immune function and that the bactericidal effect on *Porphyromonas gingivalis* is depressed in humans (10). A recent study showed that hyperlipidemia is associated with periodontal disease in animal models and several epidemiological studies have examined this. Noack et al. (48) studied 100 subjects and suggested that hyperlipidemia is a risk factor for periodontal disease, while impaired glucose tolerance is not. Losche et al. (37) reported a

case-control study indicating that total cholesterol, low-density lipoprotein cholesterol, and triglyceride were significantly higher in subjects with periodontal disease. Katz et al. (29) studied approximately 10,000 subjects and reported a higher prevalence of increased total cholesterol and low-density lipoprotein cholesterol in subjects with a higher CPI code. Since these studies were cross-sectional, it has been suggested that periodontal disease is a possible risk factor for hyperlipidemia. Subcutaneous injection and implantation of lipopolysaccharide increases the serum level of triglyceride in rats (76). Very small amounts of cytokines, such as interleukin-1 and interleukin-2, have a negative effect on lipid metabolism. Since these substances are induced in periodontal disease, it is possible that periodontal disease affects lipid metabolism. Cutler and Iacopino (10) reported that periodontal tissue infected by *P. gingivalis* increased serum triglyceride levels, but not serum glucose levels.

At present, it is not clear if periodontal disease affects lipid metabolism or whether abnormalities in lipid metabolism or conditions related to dyslipidemia cause the deterioration in the periodontal tissues. As shown in the next section, metabolism of both lipids and glucose is closely associated with liver function and the liver is a major site of lipid and glucose metabolism. It would be noteworthy to determine whether the negative effects of periodontal disease act on lipid metabolism before they act on glucose control.

Liver and periodontal disease

The liver has an important role in maintaining the blood glucose level to sustain physical function, including brain function. As a result of its anatomic position, the liver is the first organ to utilize glucose, which reaches it via the portal vein after it is absorbed in the digestive tract; it is also the main site of insulin action, which is secreted from the pancreas. After a meal, the liver converts some of the absorbed glucose into glycogen, and releases the rest into the systemic circulation. Therefore, a decrease in glucose intake by the liver leads to hyperglycemia after meals, i.e. glucose intolerance. The glycogen stores in the liver are depleted within 1 day once the production of glucose from glycogen starts; subsequently, glyconeogenesis involving the conversion of lipids is enhanced to maintain the blood glucose level. Free fatty acids from the diet and from the decomposition of triglycerides in adipocytes, flow into the liver via the

portal vein. This is then converted into energy, although some is converted into very low-density lipoprotein via triglycerides and released into the bloodstream (6). Consequently, the liver plays a very important role in glucose and lipid metabolism. Although the mechanism for the development of non-alcoholic steatohepatitis, which is frequently accompanied by obesity or diabetes, is not clear, it has been suggested that there is an association with lipopolysaccharide, which is an endotoxin of gram-negative microorganisms (15, 41, 86). Lipopolysaccharide triggers the production of various cytokines that affect lipid metabolism, leading to dyslipidemia (15, 23). The anti-lipopolysaccharide immunoglobulin G levels of subjects with periodontal disease are elevated (14, 61), and some studies have suggested a relationship between hyperlipidemia and periodontal disease (10, 11, 29, 37, 48). Tumor necrosis factor- α mediates endotoxin-induced injury in various organs and periodontal tissue (19). Of these organs, the liver is most involved in lipid metabolism. Recently, adipose tissue was shown to secrete tumor necrosis factor- α , which causes liver injury in obese rodents (86). Moreover, tumor necrosis factor- α from adipose tissue was reported to be directly associated with insulin resistance (24, 77). An increase in hepatic triglycerides is dependent on the influx of free fatty acids, which are mainly derived from visceral adipose tissue, and this is associated with insulin resistance (31). Several studies have indicated that hyperlipidemia frequently accompanies infectious diseases (15, 23). A single dose of bacterial endotoxin (lipopolysaccharide) can induce changes in lipid metabolism in adipose tissue and in the liver (15). As mentioned previously, an association between periodontitis and hyperlipidemia has been reported. Moreover, periodontal treatment decreases the serum level of glycosylated hemoglobin and has a beneficial effect on diabetic control (21, 22). If lipopolysaccharide derived from gram-negative bacteria in periodontal pockets mediates tumor necrosis factor- α release from adipose tissue, it may be associated with hepatic dyslipidemia. This hypothesis is supported by our study, in which periodontal disease was associated with the results of blood tests, especially those associated with liver function; the subjects with deep pockets had elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and cholinesterase, and an aspartate aminotransferase-to-alanine aminotransferase ratio less than one, suggesting that they have a tendency toward steatohepatitis (59). It is possible that lipopolysaccharide from periodontal pathogens affects

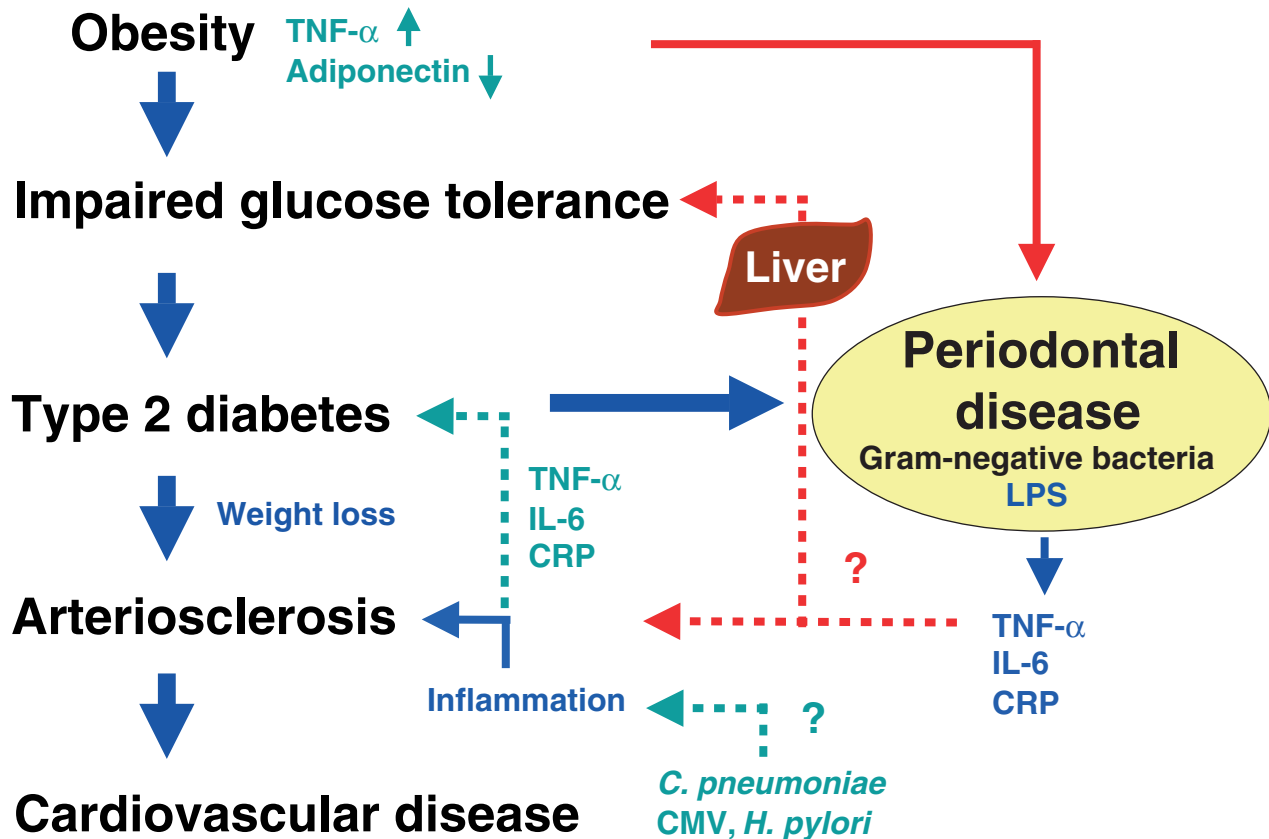


Fig. 5. Relationship between the development of obesity-related disease and periodontal disease. The blue arrows indicate established relationships. Red and green arrows indicate associations from recent reports. TNF- α , tumor

necrosis factor- α ; IL-6, interleukin-6; CRP, C-reactive protein; LPS, lipopolysaccharide; *C. pneumoniae*, *Chlamydia pneumoniae*; CMV, cytomegalovirus; *H. pylori*, *Helicobacter pylori*.

the liver, leading to hepatic dyslipidemia and glucose intolerance.

Concluding remarks

We propose the scheme illustrated in Fig. 5. The left stream with blue arrows illustrates current knowledge that includes much evidence that obesity affects type 2 diabetes and that the diabetic condition influences arteriosclerosis and cardiovascular disease. Recent evidence clarified that arteriosclerosis includes some inflammatory changes and that inflammation has a considerable effect on cardiovascular disease and type 2 diabetes. Periodontal disease is a common chronic inflammatory disease caused by gram-negative pathogens, which have a very high prevalence in adults when non-severe cases are included. The red arrows show the proposed relationships connecting periodontal disease and systemic disorders from recent studies, but these lack sufficient supporting evidence at present. Reports on

the relationship between obesity and periodontal disease are increasing and the relationship in young adults is likely to be major. However, all of these studies are cross-sectional or case-control studies. Prospective cohort studies and laboratory studies are required to clarify whether obesity is one of the risk factors for periodontal disease or simply a risk indicator.

Recent studies suggest that periodontal disease affects glucose metabolism in both diabetics and non-diabetics. Considering the relationship between obesity and periodontal disease and the strong causal relationship between obesity and diabetes, we can only conclude that the associations among periodontal disease, diabetes, and obesity confound each other. More studies on the causal relationships among these three health disorders with stringent consideration of confounders are needed.

Associations between lipid metabolism and hepatic disorders with periodontal disease have emerged. These are strongly associated not only with obesity, but also with glucose metabolism, especially in the

liver. They may become a key to clarifying the metabolic disorders related to periodontal disease.

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