Obesity, Inflammation, and Periodontal Disease

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ABSTRACT

The prevalence of obesity has increased substantially over the past decades in most industrialized countries. Obesity is a systemic disease that predisposes to a variety of comorbidities and complications that affect overall health. Cross-sectional studies suggest that obesity is also associated with oral diseases, particularly periodontal disease, and prospective studies suggest that periodontitis may be related to cardiovascular disease. The possible causal relationship between obesity and periodontitis and potential underlying biological mechanisms remain to be established; however, the adipose tissue actively secretes a variety of cytokines and hormones that are involved in inflammatory processes, pointing toward similar pathways involved in the pathophysiology of obesity, periodontitis, and related inflammatory diseases. We provide an overview of the definition and assessment of obesity and of related chronic diseases and complications that may be important in the periodontist's office. Studies that have examined the association between obesity and periodontitis are reviewed, and adipose-tissue-derived hormones and cytokines that are involved in inflammatory processes and their relationship to periodontitis are discussed. Our aim is to raise the periodontist's awareness when treating obese individuals.

KEY WORDS: obesity, adipose tissue, inflammation, periodontal disease.

INTRODUCTION

Obesity, defined as a body mass index (BMI) ≥ 30.0 kg/m², is a major public health problem today. The prevalence of obesity has increased substantially over the past decades in most industrialized countries. In the year 2004, approximately 34.1% of the US population was overweight (BMI 25.0-29.9 kg/m²), and about 32.2% obese (Fig. 1) (Expert Panel, 1998; Mokdad et al., 2003; Ogden et al., 2006). A further increase is expected in the future (Seidell, 2000). Obesity is a risk factor for several chronic diseases, most notably hypertension, type 2 diabetes, dyslipidemia, and coronary heart disease (Table 1) (Must et al., 1999; Mokdad et al., 2004; Flegal, 2006; Gregg et al., 2005). It is estimated that the costs associated with the management of obesity and obesity-related diseases account for about 5% of total healthcare expenditures in most industrialized countries (Thompson and Wolf, 2001). The relevance and consequences of the obesity epidemic have long been recognized by the scientific community and public health policymakers, and expert committees have made recommendations on how to assess, prevent, and treat the obesity epidemic (Expert Panel, 1998). Since adiposity can be considered as a systemic disease that predisposes to a variety of comorbidities and complications that affect overall health, obese persons require awareness across the spectrum of health professionals, including dentists. Further, recent studies have suggested that obesity is also associated with oral diseases, particularly with periodontitis (Perlstein and Bissada, 1977; Saito et al., 1998, 2001, 2005; Al-Zahrani et al., 2003; Wood et al., 2003; Dalla Vecchia et al., 2005; Genco et al., 2005). In fact, the adipose tissue secretes several cytokines and hormones that are involved in inflammatory processes, suggesting that similar pathways are involved in the pathophysiology of obesity and periodontitis.

The present article provides an overview of the definition and assessment of obesity and of the major chronic diseases and complications related to adiposity that may be of importance in the periodontal office. Further, we present a summary of adipose-tissue-derived hormones and cytokines that are involved in inflammatory processes, and discuss their potential impact on periodontitis. We also discuss potential effects of periodontitis-related cytokines on obesity-associated diseases, and review studies that have examined the association between obesity and periodontitis. Our aim is to raise the periodontist's awareness when treating obese individuals.

DEFINITION AND ASSESSMENT OF OBESITY

The definition of obesity is based on the body mass index (BMI, also called Quetelet Index), which is the ratio of body weight (in kg) to body height (in m) squared (Table 2) (Expert Panel, 1998). BMI is highly correlated with fat mass and morbidity and mortality, and therefore sufficiently reflects obesity-related disease risk in a wide range of populations; however, there are some limitations. For example, for the same BMI, older persons tend to have a higher body fat composition, and, therefore, risk assessment by BMI is less accurate in older people (over 65 yrs of age). Furthermore, current BMI cut-off points for overweight and obesity are probably too
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high for Asian populations (Table 2) (Choo, 2002). More importantly, the BMI does not assess body fat distribution. It is well-known that abdominal (central, visceral, android) obesity, which is usually observed in men, is associated with a higher morbidity than the gluteofemoral (peripheral, gynoid) obesity typically observed in women (Expert Panel, 1998). Body fat distribution is assessed by the measurement of waist circumference, with 102 cm in men and 88 cm in women, respectively, being the cut-off point for abdominal obesity associated with an increased risk of morbidity (Table 3) (Expert Panel, 1998). Waist circumference shows a close correlation with the amount of visceral adipose tissue, and visceral adipose tissue has been shown to be metabolically more active and to secrete far greater amounts of cytokines and hormones compared with subcutaneous adipose tissue (Pouliot et al., 1994; Wajchenberg, 2000; Berg and Scherer, 2005). Further, a higher influx of portal fatty acids, cytokines, and hormones into the liver from omental adipose tissue may specifically distort hepatic metabolism, including abnormal lipoprotein synthesis, hepatic insulin resistance, and increased gluconeogenesis (Eckel et al., 2005; Haslam and James, 2005). Recent large studies have indicated that measurement of waist circumference or waist-hip ratio may be a better disease risk predictor than BMI (Wang et al., 2005; Yusuf et al., 2005), and there is still intensive research ongoing as to whether BMI, waist circumference, or both should be used to assess disease risk. Several other diagnostic tools are available to assess body fat composition, such as measurement of (subcutaneous) skin fold by means of a caliper or ultrasound, bioelectrical impedance analysis (BIA), densitometry, or imaging procedures (CT, NMR); however, most of these procedures are not readily available in clinical practice, and do not add substantial information for risk assessment in an individual beyond BMI and waist circumference (Heymsfield et al., 1998).

**Figure 1.** Prevalence of overweight and obesity in the United States (US) and in Europe. Numbers in parentheses indicate year of data assessment. Data for the US are from the National Health and Nutrition Examination Survey, 2003-2004, with measured height and weight, as provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/; accessed April 28, 2006) (Ogden et al., 2006). Data for Europe are from the national Health Interviews Surveys, round 2004, as provided by Eurostat, the official European Union’s statistical information service (http://epp.eurostat.cse.eu.int; accessed April 26, 2006). In addition to year of data collection, age range in surveys may differ. Weight and height are based on self-reports of participants in most countries, except the United States, Germany, and the United Kingdom, where height and weight were measured.


<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Type 2 diabetes</td>
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<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Coronary heart disease</td>
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<tr>
<td>Stroke</td>
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<td>Gallbladder disease</td>
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<td>Liver disease (non-alcoholic steatohepatitis)</td>
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<td>Musculoskeletal disease (osteoarthritis)</td>
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<tr>
<td>Sleep apnea and pulmonary dysfunction</td>
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<tr>
<td>Cancer (colon cancer, endometrial cancer, post-menopausal breast cancer, kidney cancer)</td>
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<tr>
<td>Reproductive abnormalities (menstrual irregularities, infertility)</td>
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</tbody>
</table>

* The list is based on reviews by experts and expert committees about obesity and its relation to chronic disease incidence. Sufficient evidence indicates that associations between obesity and chronic disease risk were observed in several prospective studies in different populations and are supported by experimental models.

**OBESITY-RELATED DISEASES**

**Hypertension**

Overweight and obesity have long been recognized as important determinants of elevated blood pressure levels (Must et al., 1999). It is well-established that weight gain is consistently associated with increased blood pressure, and that weight loss decreases blood pressure independent of changes in sodium intake. Compared with normal-weight individuals, obese persons have an up to 5 times higher risk of hypertension, and up to 2/3 of cases of hypertension can be attributed to excess weight (Wolf et al., 1997). Mechanisms that have been implicated in the development of obesity-related hypertension include increased sympathetic nerve activity,
Table 2. Classification and Definition of Overweight and Obesity (based on Expert Panel, 1998)*

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Men ≤ 102 cm Women ≤ 88 cm</th>
<th>Men &gt; 102 cm Women &gt; 88 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
<td>High</td>
</tr>
<tr>
<td>Obese - Class I</td>
<td>30.0-34.9</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>Obese - Class II</td>
<td>35.0-39.9</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Obese - Class III</td>
<td>≥ 40</td>
<td>Extremely high</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

* Established for non-Asian populations. The recently proposed classification for Asian populations is: BMI < 18.5, underweight; 18.5-22.9, normal weight; 23.0-24.9, overweight; 25.0-29.9, obese class I; ≥ 30.0, obese class II (WHO/IASO/IOTF, 2000).
† Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

Table 3. Definition of the Metabolic Syndrome Based on the NCEP-ATP III Definition

<table>
<thead>
<tr>
<th>Risk Factor*</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>Men &gt; 102 cm</td>
<td>Women &gt; 88 cm</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Men &lt; 40 mg/dL</td>
</tr>
<tr>
<td>Women &lt; 50 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥ 130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 110 mg/dL</td>
</tr>
</tbody>
</table>


sodium and volume retention, renal abnormalities, insulin resistance, hyperleptinemia, and increased secretion of angiotensinogen from adipocytes (Kolanowski, 1999; Haslam and James, 2005).

Type 2 Diabetes

The relationship between obesity and type 2 diabetes is particularly close. Obese persons have a more than 10-fold increased risk of developing type 2 diabetes compared with normal-weight persons (Field et al., 2001). Type 2 diabetes develops due to an interaction between insulin resistance and beta cell failure (Stumvoll et al., 2005). Several factors, including lipotoxicity and glucose toxicity as well as obesity-derived cytokines, have been implicated in these processes (Stumvoll et al., 2005).

Cardiovascular Disease and the Metabolic Syndrome

Obese persons have an about 1.5-fold increased risk for cardiovascular disease (including coronary heart disease and cerebrovascular disease), and between 10 and 15% of all cases of cardiovascular disease can be attributed to overweight and obesity (Wilson et al., 2002). The association with obesity is slightly stronger, and the population-attributable fraction (PAF, i.e., the fraction of cases within the population that can be attributed to overweight and obesity) larger, for coronary heart disease (relative risk about 1.5 to 2.0; PAF 15 to 20%) than for cerebrovascular disease (RR 1.2 to 1.8; PAF 5 to 15%) (Field et al., 2001; Wilson et al., 2002). Obesity is also associated with an about two-fold higher risk of heart failure and a 50% increased risk of atrial fibrillation (Kenchaiah et al., 2002).

The metabolic syndrome is a concept that encompasses metabolic abnormalities that co-occur to a greater degree than would be expected by chance alone, and which predispose individuals for a high risk to develop cardiovascular disease (Eckel et al., 2005). The World Health Organization (WHO), the National Cholesterol Education Program (NCEP), and the International Diabetes Federation (IDF) have proposed algorithms to define the metabolic syndrome (WHO, 1999; Executive Summary of The Third Report of The National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], 2001; International Diabetes Federation, 2005). Although slightly different in detail, these definitions agree on the essential components, namely, glucose intolerance, obesity, hypertension, and dyslipidemia (albeit the WHO also includes microalbuminuria as a component) (WHO, 1999; International Diabetes Federation, 2005). To date, most studies have used the definition provided in the “Third Report of the National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP-ATP III)”, which requires the presence of at least three of the following metabolic abnormalities before the metabolic syndrome can be defined: abdominal obesity, elevated triglycerides, reduced levels of HDL cholesterol, high blood pressure, and high fasting glucose (Table 3) (Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], 2001). Based on this definition, the prevalence of the metabolic syndrome was estimated to be around 23% in the United States (Ford et al., 2002).

Although the exact underlying cause of the metabolic syndrome is unknown, the more recent definitions emphasize the focus on abdominal obesity as its core component (International Diabetes Federation, 2005). This approach is supported by a growing number of studies showing that the adipose tissue itself is capable of producing several hormones and proteins, which are involved in the development of obesity-related diseases (see below).

Other Diseases and Mortality

Sufficient evidence exists that obesity also increases the risk of respiratory disorders, reproductive abnormalities, non-alcoholic steatohepatitis, gallbladder disease, osteoarthritis, and certain types of cancer (see Table 1). Whether overweight and obesity affect disease prognosis and total mortality is an ongoing area of research, and recently published studies have found contradictory results (Mokdad et al., 2004; Flegal et al., 2005).
For example, although obesity increases the risk of heart failure, the studies found that, among persons with prevalent heart failure, obese individuals are likely to have a better prognosis than non-obese individuals (Curtis et al., 2005). This is likely due to the fact that lower BMI reflects wasting processes in this patient group (as in other chronic diseases). Further, several studies have found a U-shaped association between BMI and total mortality, with a minimum at a BMI of approximately 25.0 kg/m² and increased mortality with higher or lower BMI (Troiano et al., 1996; Calle et al., 1999; Flegal et al., 2005). However, it has been argued that these analyses may be confounded by smoking (smokers are usually leaner than non-smokers but have a higher risk of mortality) or underlying prevalent chronic diseases (individuals with chronic diseases often have lower body weight) (Willett et al., 2005). Clearly, further studies are needed to examine the effect of obesity on morbidity, disease prognosis, and mortality.

**ASSOCIATION BETWEEN OBESITY AND PERIODONTAL DISEASE**

It has been suggested that obesity is second only to smoking as the strongest risk factor for inflammatory periodontal tissue...

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**Table 4. Epidemiological Studies Analyzing the Association between Obesity and Periodontal Disease***

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Age Range (yrs)</th>
<th>Assessment of Periodontitis</th>
<th>No. of Cases with Periodontitis</th>
<th>Outcome</th>
<th>OR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>241 apparently healthy dentulous Japanese persons (69 men, 172 women) who attended a health promotion program, Fukuoka Health Promotion Center</td>
<td>20-59</td>
<td>CPITN code 3 or 4, PPD ≥ 4 mm</td>
<td>96</td>
<td>BMI</td>
<td>&lt; 20.0, 1 (reference), 20.0-24.9, 1.7 (0.7-3.8), 25.0-29.9, 3.4 (1.2-9.6), ≥ 30.0, 8.6 (1.4-51.4)</td>
<td>Saito et al., 1998</td>
</tr>
<tr>
<td>643 apparently healthy dentulous Japanese persons (131 men, 512 women) who attended a health promotion program, Fukuoka Health Promotion Center</td>
<td>19-79</td>
<td>At least one tooth per sextant with PPD ≥ 4 mm</td>
<td>334</td>
<td>WHR, men/women</td>
<td>&lt; 0.9/0.8, 1 (reference), ≥ 0.9/0.8, 2.0 (1.4-2.9)</td>
<td>Saito et al., 2001</td>
</tr>
<tr>
<td>584 Japanese women with at least 10 teeth, Hisoyama study</td>
<td>40-79</td>
<td>Mean PPD ≥ 1.9 mm</td>
<td>114</td>
<td>BMI</td>
<td>15.5-20.8, 1 (reference), 20.8-22.7, 3.0 (1.4-6.3), 22.7-24.9, 2.3 (1.1-5.0), 25.0-46.7, 4.3 (2.1-8.9)</td>
<td>Saito et al., 2005</td>
</tr>
<tr>
<td>US general population, Third National Health and Nutrition Examination Survey (NHANES III), restricted to persons ≥ 18 yrs with periodontal examination; n = 13,665 (6466 men, 7199 women)</td>
<td>≥ 18</td>
<td>Presence of one or more sites with CAL of ≥ 3 mm and PPD ≥ 4 mm</td>
<td>2560</td>
<td>BMI</td>
<td>&lt; 18.5, 0.79 (0.42-1.49), 18.5-24.9, 1.06 (0.91-1.24), ≥ 30, 1.37 (1.14-1.64),</td>
<td>Al-Zahrani et al., 2003; the relationship of parameters of obesity and insulin resistance with periodontal disease within this population is further described by Genco et al. (2005) and Wood et al. (2003)</td>
</tr>
<tr>
<td>372 Japanese factory workers (290 men, 82 women)</td>
<td>20-59</td>
<td>proportion of teeth with PPD &gt; 3.5 mm being beyond the 20th percentile within this population</td>
<td>74</td>
<td>BMI</td>
<td>&lt; 25.0, 1 (reference), ≥ 25.0, 3.17 (1.79-5.61)</td>
<td>Nishida et al. (2005)</td>
</tr>
<tr>
<td>706 South Brazilian individuals (329 men, 377 women) drawn randomly from a larger representative sample of Porto Alegre</td>
<td>30-65</td>
<td>≥ 30% of teeth with CAL ≥ 5 mm</td>
<td>298</td>
<td>BMI</td>
<td>men: 18.5-24.9, 1 (reference), ≥ 25.0, 1.1 (0.4-3.3), women: 18.5-24.9, 1 (reference), ≥ 25.0, 1.3 (0.8-2.2), ≥ 30.0, 2.1 (1.1-3.9)</td>
<td>Dalla Vecchia et al. (2005)</td>
</tr>
</tbody>
</table>

* All studies used a cross-sectional design. Studies were adjusted for age, gender, smoking history, socio-economic status, and oral hygiene. BMI, body mass index; WHR, waist-hip ratio; CPITN, Community Periodontal Index of Treatment Needs; CAL, Clinical attachment loss; OR, odds ratio; PPD, Periodontal pocket depth.
The first report on the relationship between obesity and periodontal disease appeared in 1977, when Perlstein et al. observed histopathologic changes in the periodontium in hereditary obese Zucker rats (Zucker and Zucker, 1962; Perlstein and Bissada, 1977). Using ligature-induced periodontitis, they found alveolar bone resorption to be greater in obese animals compared with non-obese rats (Perlstein and Bissada, 1977). Also, it seemed that, under healthy oral conditions, obesity per se does not promote pathologic periodontal alterations; however, in response to bacterial plaque accumulation, periodontal inflammation and destruction were more severe in obese animals. In obese and hypertensive rats, plaque accumulation caused even more pronounced periodontal destruction than in obese animals, suggesting that a combination of risk factors, such as those defined by the metabolic syndrome, elicit the most severe periodontal effects (Koletsky, 1973; Perlstein and Bissada, 1977).

Later on, the hypothesis of obesity as a risk factor for periodontal disease was supported by epidemiological studies (Table 4). Besides one study performed in a Brazilian population, the majority of reports of association between BMI and periodontitis are primarily based on analyses of Japanese populations and US data from the Third National Health and Nutrition Examination Survey (NHANES III). Also, variability exists in the definition of the periodontal disease reported.

In 1998, Saito et al. analyzed 241 healthy Japanese individuals and showed, for the first time, an association between obesity and periodontal disease in humans (Saito et al., 1998). They applied the community periodontal index of treatment needs (CPITN) and estimated, based on their cross-sectional analysis, that the relative risk for periodontitis after adjustment for confounders such as age, gender, oral-hygiene status, and smoking was 3.4 in persons with BMI of 25 to 29.9 kg/m², and 8.6 in those with BMI above 30 kg/m².

In addition, studies have indicated that the fat distribution pattern plays a crucial role in the association with periodontitis (Saito et al., 2001; Al-Zahrani et al., 2003; Wood et al., 2003). Saito et al. found, in 643 healthy Japanese adults, that high upper body obesity and high total body fat were correlated with a higher risk of periodontal disease, compared with normal-weight persons (Saito et al., 2001). An examination of the NHANES III data demonstrated that waist-to-hip ratio, BMI, fat-free mass, and log sum of subcutaneous fat significantly correlated with periodontal disease (Wood et al., 2003). Also, high waist circumference was especially associated with periodontal disease in 18- to 34-year-old persons, but not in older adults, suggesting a closer correlation between high waist circumference and periodontitis in young adults (Al-Zahrani et al., 2003). In 706 South Brazilian individuals, no correlation between BMI and periodontal disease was found in men, but a strong correlation was found in obese females (Dalla Vecchia et al., 2005).

Another recent study by Saito et al. concluded that obesity is associated with deep periodontal pockets, independent of glucose tolerance status (Saito et al., 2005). Genco et al. analyzed NHANES III data and demonstrated that BMI was positively correlated with the severity of periodontal attachment loss; they found that this relationship is modulated by insulin resistance (Genco et al., 2005).

Recent studies have indicated that maintaining a normal weight by regular physical activity is associated with a lower periodontitis prevalence (Wakai et al., 1999; Karjalainen et al., 2002; Merchant et al., 2003; Al-Zahrani et al., 2005a,b). Individuals who pursued regular exercise have lower plasma levels of inflammatory markers, such as IL-6 and C-reactive protein (CRP), and show an increased insulin sensitivity that may beneficially affect periodontal health (Merchant et al., 2003; Pischon et al., 2003; Al-Zahrani et al., 2005a). A study that analyzed the NHANES III study population demonstrated that individuals who maintained a normal weight, pursued regular exercise, and consumed a diet in conformity with the Dietary Guidelines for Americans and the Food Guide Pyramid recommendations were 40% less likely to have periodontitis (Al-Zahrani et al., 2005a).

The results of the currently published cross-sectional studies indicate an association between obesity and periodontal disease. However, some limitations must be considered. First, the design of these studies limits interpretability about temporal relationships. Because anthropometry and dental status were assessed simultaneously, it is unclear whether obesity truly precedes periodontitis. Prospective cohort studies may circumvent this problem. For example, by enrolling individuals without periodontitis into a cohort, one could assess whether obese participants are more likely to develop periodontitis over time than non-obese participants. Second, observational studies can show only associations, but not causal effects. Although adjustment for factors related to obesity and known to affect the risk of periodontitis (e.g., socio-economic status) may reduce confounding in these observational studies (listed in Table 4), the observed association may be caused by unidentified underlying factors. Interventional studies (Randomized Controlled Trials) may be the gold standard for Evidence-based Dental Medicine; however, such studies may be difficult to conduct, given that obesity is the exposure variable of interest. One alternative approach would be to examine whether a weight-loss intervention in obese individuals may beneficially affect periodontal disease. However, the long-term success of weight loss achieved by caloric restriction or increased physical activity is questionable, and additional anti-obesity drug therapy or anti-obesity surgery may be necessary (Expert Panel, 1998).

The underlying biological mechanisms for the association of obesity with periodontitis are not well-known; however, adipose-tissue-derived cytokines and hormones may play a key role. Fat tissue is not merely a passive triglyceride reservoir of the body, but also produces a vast amount of cytokines and hormones, collectively called adipokines or adipocytokines (Kershaw and Flier, 2004), which in turn may modulate periodontitis.

**ADIPOSE-TISSUE-DERIVED HORMONES AND CYTOKINES (ADIPOKINES)**

**Inflammatory Markers**

Adipose tissue secretes pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6). TNF-α and IL-6 are the main inducers of acute-phase hepatic protein production, including CRP (Yudkin et al., 2000). Both TNF-α and IL-6 have been shown to impair intracellular insulin signaling, which may lead to insulin resistance (Hotamisligil, 2000; Rotter et al., 2003). In humans,
plasma levels of TNF-α, IL-6, and CRP are closely related to obesity and insulin resistance (Hotamisligil, 1999; Kern et al., 2001). There is compelling evidence that inflammation plays an essential role in the development of type 2 diabetes mellitus and atherosclerosis, and studies in humans suggest that circulating inflammatory marker levels may predict type 2 diabetes and cardiovascular events years in advance of the onset of these diseases (Pradhan et al., 2001; Libby, 2002; Pradhan and Ridker, 2002; Ridker, 2002; Danesh et al., 2004; Pai et al., 2004).

Periodontitis is a chronic inflammatory disease of periodontal tissues (Offenbacher, 1996). Some individuals are more susceptible and exhibit a greater degree of periodontal infection and inflammation (Beck et al., 1996, 1998). An up to 10-fold increase in local and systemic expression of inflammatory cytokines, such as TNF-α and IL-6, by monocytes and macrophages has been reported in some individuals with periodontitis (Beck et al., 1996). In persons with periodontitis, bacterial pathogens, endotoxins, and inflammatory cytokines may systemically trigger an up-regulated leukocytosis, synthesis of acute-phase proteins (CRP, Amyloid A), and enhanced lipid metabolism, along with increased serum cholesterol and triglyceride levels, which may contribute to the risk of systemic diseases such as cardiovascular diseases (Beck et al., 1998; Loos et al., 1998; Nishimura et al., 2003; Beck and Offenbacher, 2005; Loos, 2005; Mattila et al., 2005).

Leptin

Leptin is a pleiotropic cytokine, secreted by adipocytes, which is involved in a variety of biological processes, including energy metabolism, endocrine functions, reproduction, and immunity (Zhang et al., 1994). Leptin is thought to act as a "lipostat" that regulates adipose tissue mass. As a negative feedback mechanism, elevated leptin concentrations result in increased energy expenditure, decreased food intake, and a negative energy balance (Kennedy, 1953; Friedman, 1998). Leptin deficiency caused by mutations in the ob gene encoding leptin (which are only rarely observed in humans) results in increased energy expenditure, decreased food intake, and a "lipostat" that regulates adipose tissue mass. As a negative energy balance (Kennedy, 1953; Friedman, 1998).

Adiponectin, Resistin, and Other Adipose-tissue-derived Cytokines

Adiponectin is a circulating hormone secreted by adipose tissue that is involved in glucose and lipid metabolism, and which accounts for about 0.05% of total serum proteins (Berg et al., 2002; Chandran et al., 2003). Contrary to other adipose-derived hormones, adiponectin levels are reduced in persons with obesity, insulin resistance, or type 2 diabetes (Berg et al., 2002; Chandran et al., 2003). Adiponectin improves insulin sensitivity and may have anti-atherogenic and anti-inflammatory properties (Ouchi et al., 2000, 2001; Arita et al., 2002; Kubota et al., 2002), and low plasma adiponectin levels have been shown to predict type 2 diabetes and coronary heart disease in humans (Berg et al., 2001; Yamauchi et al., 2001; Lindsay et al., 2002; Maeda et al., 2002; Spranger et al., 2003; Pischon et al., 2004). Experimental models suggest that adiponectin could play a role as a mediator of inflammation; however, the exact role of adiponectin in inflammatory diseases remains to be elucidated (Ouchi et al., 2000; Maeda et al., 2002).

Resistin belongs to a family of resistin-like molecules (RELM) and has been reported to be secreted by adipocytes and to cause insulin resistance in animal models (Steppan et al., 2001a,b; Rajala et al., 2002). However, studies have shown that the biology of resistin differs substantially between species, and many aspects, specifically its association with obesity and its effects on insulin sensitivity in humans, remain controversial. Thus, in contrast to mice, human resistin is expressed at lower levels in adipocytes, but at higher levels in circulating blood monocytes (Nagaev and Smith, 2001; Savage et al., 2001), and current evidence suggests that, in humans, resistin is more closely related to inflammatory processes than to insulin resistance (Verma et al., 2003; Kawanami et al., 2004). Interestingly, the amino acid sequences of resistin and of RELMα and RELMb are identical to the previously discovered proteins FIZZ3, FIZZ1, and FIZZ2, respectively, which are involved in inflammatory processes (Holcomb et al., 2000; Gomez-Ambrosi and Fruhbeck, 2001), and elevated resistin levels were found in persons with coronary heart disease (Pischon et al., 2005; Burnett et al., 2006). Whether or not resistin plays a role in inflammatory periodontal disease remains to be defined.

As more and more adipose-tissue-derived cytokines and hormones are being discovered, the complexity of the endocrine network of which these mediators are a part becomes more and more apparent. Recent additions to this list of adipokines include visfatin, which elicits insulin-like effects, and serum-retinol-binding protein 4 (RBP4) (Fukuhrana et al., 2005; Yang et al., 2005). Regarded initially as markers mainly related to weight regulation and insulin resistance, it has become clear that hormones like leptin, resistin, or adiponectin...
are involved in a variety of functions and diseases (see above), including cardiovascular disease, diabetes, and inflammatory diseases (Otero et al., 2005).

ASSOCIATION OF PERIODONTITIS WITH OBESITY-RELATED CHRONIC DISEASES

Pro-inflammatory cytokines may play a crucial role in the close relationship among periodontitis, obesity, and chronic diseases (Beck and Offenbacher, 2005; Gencor et al., 2005). In fact, this association may be multidirectional (Fig. 2). For example, it has been well-established that inflammation is an essential component in the development of atherosclerosis, and observational studies showed that periodontitis is associated with a moderately, but significantly, higher risk of coronary heart disease (Beck and Offenbacher, 2005; Dietrich and Garcia, 2005; Mattila et al., 2005). Interventional studies that examined the effects of antibiotic treatment on cardiovascular risk have generally failed to show any beneficial effect; however, these studies have mostly been of short duration (less than 1 year of treatment) and have investigated the effects on secondary prevention only. Inflammatory diseases like periodontitis induce the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (Beck et al., 1996; Loos, 2005). It has been suggested that the secretion of TNF-α by adipose tissue triggered by LPS from periodontal Gram-negative bacteria promotes hepatic dyslipidemia and decreases insulin sensitivity (Saito et al., 2001; Nishimura et al., 2003). Type 2 diabetes and decreased insulin sensitivity are associated with the production of advanced glycation end-products (AGE), which trigger inflammatory cytokine production, thus predisposing for inflammatory diseases such as periodontitis (Grossi and Genco, 1998; Gencor et al., 2005). These observations suggest a potential interaction among obesity, periodontitis, and chronic disease incidence, although present studies are insufficient to conclude whether such associations are causal. Thus, in addition to being a risk factor for type 2 diabetes and coronary heart disease, obesity-related inflammation may also promote periodontitis. Conversely, periodontitis, once it exists, may promote systemic inflammation and thereby increase the risk of coronary heart disease (Beck and Offenbacher, 2005; Loos, 2005). In this context, it is interesting to note that periodontal treatment has been shown to reduce circulating TNF-α and serum levels of glycosylated hemoglobin, and has beneficial effects on the control of type 2 diabetes (Grossi and Genco, 1998).

RISK AND RISK ASSESSMENT IN THE PERIODONTAL OFFICE

When one considers that more than 60% of the US population is overweight or obese (and the numbers are rising), treating overweight persons in the dental office will become more and more common.

Until recently, a definite diagnosis of obesity was only rarely made by physicians, and body weight or body height was rarely measured in clinical practice (Linn and Rossner, 1998; Cleator et al., 2002). Further, it has been shown that about 25% of obese persons have been misclassified, by subjective estimation of the physician, as having normal weight (Caccamese et al., 2002). In the future, if obesity is to be acknowledged as a multiple-risk-factor syndrome for overall and oral health, general and oral risk assessment in the dental office should include the evaluation of body mass index on a regular basis. Although there is still research ongoing as to whether BMI or waist circumference, or both, is a better disease risk predictor, the assessment of waist circumference in addition to BMI seems advisable, based on current obesity guidelines. Besides the suggested association between periodontal disease and obesity, periodontists need to be aware of the potential health problems related to obesity, and should take them into account during treatment. For example, pain and anxiety trigger the release of catecholamines, resulting in peripheral vasconstriction and further diminished tissue oxygenation (Wilson and Clark, 2004). Co-existent coronary heart disease or type 2 diabetes in obese individuals may lead to acute angina or to hyper- or hypoglycemia during dental treatment. Due to the person's overweight, which prevents full expansion of the lungs, an obesity-hypoventilation syndrome can develop and cause hypercapnia, hypoxia, somnolence, hypoxic pulmonary vasconstriction, pulmonary hypertension, and right-sided heart failure (Kempers et al., 2000). Therefore, it has been suggested that supine patient positioning should be avoided, to maximize the pulmonary mechanics (Kempers et al., 2000). Impaired chest expansion decreases vital capacity and tidal function, which compromise tissue oxygenation (Wilson and Clark, 2004). These conditions put the obese person at high anesthetic and surgical risk (Kempers et al., 2000). Wound-healing processes are dependent on sufficient tissue oxygenation (Armstrong, 1998). Also, higher incidences of infections and post-surgical hematoma formation have been reported among obese persons (Wilson and Clark, 2004). The vulnerability to wound complications increases not only morbidity and mortality of obese persons, but also the length of individual treatment sessions, the overall length of the treatment, and, consequently, the economic costs of treatment (Wilson and Clark, 2004). Pharmacological aspects, such as altered pharmacokinetics due to the person's increased blood volume or fat mass, and technical incompatibilities, such as small dental chairs or tight blood pressure cuffs, should be considered (Kempers et al., 2000). Kempers et al. have emphasized the importance of details in the individual's medical and dental history when overweight persons present to
the office, to keep complications during and after the dental treatment to a minimum (Kempers et al., 2000). They proposed to ascertain, in individuals, symptoms of general fatigue, weakness, and sleep disturbances, which may be signs of obstructive sleep apnea. Also, chest pain, shortness of breath, dyspnea on exercise, and peripheral edema could indicate compromised cardiac function. Persons should be questioned about symptoms of diabetes, such as polyuria, polydipsia, or polyphagia. Also, a close collaboration with the general physician and the dietician may be beneficial to ensure effective periodontal treatment.

**SUMMARY**

Periodontists must be aware of the increasing numbers of obese persons and of the significance of obesity as a multiple-risk-factor syndrome for overall and oral health. Recent cross-sectional and prospective studies have indicated a close correlation of obesity with periodontal disease and with other chronic inflammatory diseases, including type 2 diabetes and cardiovascular disease. Whether the relationship between obesity and periodontitis is causal needs to be assessed in future studies. Pro-inflammatory cytokines may be a multidirectional link among periodontitis, obesity, and other chronic diseases. The adipose tissue is a large reservoir of biologically active mediators, such as TNF-α and other adipokines. Studies have demonstrated a close involvement of the adipokines—such as leptin, resistin, and adiponectin—in inflammatory processes. However, their role in periodontal inflammation has yet to be defined.

Obesity is a complex disease, and its relationship to oral status has been realized by the scientific community in recent years. Although this relationship needs further investigation, periodontists should counsel obese persons regarding the possible oral complications of obesity, to diminish morbidity for these individuals. This includes the measurement of body mass index and waist circumference for periodontal risk assessment on a regular basis.

**REFERENCES**


