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ABSTRACT

Sex-specific differences in the incidence of periodontitis and tooth loss may be related to different phenotypes of obesity and their associations with low-grade inflammation. The aim of this study was to evaluate associations of adiposity and low-grade inflammation with tooth loss in men and women. Follow-up data of 2,714 participants from the cohort of Study of Health in Pomerania were analyzed for anthropometric measures, periodontitis, tooth loss, C-reactive protein (CRP), and interleukin 6. Regression analyses were used to estimate the effect of obesity on tooth loss within sex strata. During the follow-up period, men lost more teeth in relation to their obesity status than did women. In contrast, there was a steeper increase in CRP levels across obesity levels in women as compared to men. Incidence rate ratio (IRR) of tooth loss associated with elevated CRP, however, was higher in men (IRR = 1.50; 95% confidence interval [CI]: 1.27, 1.77) than women (IRR = 1.18; 95% CI: 1.02, 1.37). Negative binomial regression with number of lost teeth as outcome revealed dose-response dependencies on body mass index and waist-to-hip ratio. Adjusted for covariates, the IRR of tooth loss associated with the third tertile of waist-to-hip ratio was 1.37 (95% CI: 1.04, 1.80) and 1.53 (95% CI: 1.14, 2.05) in men and women, respectively. Tooth loss related to CRP cutoff of 2 mg/L was significant in men (IRR = 1.33; 95% CI: 1.07, 1.66; $p = .006$) but not in women (IRR = 0.92; 95% CI: 0.73, 1.17; $p = .689$). This study suggests that both adiposity and subclinical inflammation affect tooth loss, with distinct differences between men and women. Obesity as a risk factor of tooth loss is particularly related to CRP in men but not in women.

KEY WORDS: periodontitis, C-reactive protein, adiposity, risk factors, follow-up-study, population groups.

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Sex Differences of Tooth Loss and Obesity on Systemic Markers of Inflammation

INTRODUCTION

Obese individuals have an increased risk of multiple chronic diseases, among them periodontitis (Suvan *et al.*, 2011). Periodontitis is an inflammatory chronic disease of the gums leading to attachment loss and bone destruction. Periodontal disease eventually results in tooth loss and is associated with systemic inflammatory diseases. Elevated blood levels of inflammatory markers such as C-reactive protein (CRP) or interleukin 6 (IL-6) are commonly observed in periodontitis, indicating systemic reactions to the local inflammation within the oral cavity (Linden *et al.*, 2008). Elevated concentrations of inflammatory markers are also associated with obesity. Furthermore, obesity and elevated CRP levels are associated with many chronic diseases, such as cardiovascular diseases or diabetes (Bastard *et al.*, 2006). Likewise, a mutual relationship might exist among obesity, CRP, and periodontitis (Chaffee and Weston, 2010).

Visceral fat in obesity plays a major role in the development of metabolic disturbances associated with these systemic diseases, eventually interacting with the local inflammation in periodontal diseases. Characteristic sex differences exist with respect to the fat distribution, and such differences are known for the relationship between obesity and systemic inflammatory markers (Thorand *et al.*, 2007; Choi *et al.*, 2013). Central adiposity is most strongly associated with CRP in women, whereas percentage fat of the body composition is a stronger predictor of systemic inflammation in men (Valentine *et al.*, 2009).

Inflammatory mediators are assumed to be the connecting link between obesity and periodontitis induced indirectly via hepatic activation of the acute-phase response that leads to increased circulating levels of CRP (Pischon *et al.*, 2007). The chronic proinflammatory state with CRP being a biomarker might be the link between obesity and periodontitis finally resulting in tooth loss (Boesing *et al.*, 2009; Pradeep *et al.*, 2012). Tooth loss is the possible consequence of oral disease experiences affected by accumulated inflammatory and environmental factors. However, in both dentate and edentulous subjects devoid of periodontal inflammation, obesity contributes to increased CRP levels (Meisel *et al.*, 2012). Thus, the direction of such an interrelationship remains obscure.

The incidence of periodontal disease during a 5-yr period was reported to increase with raised body mass index (BMI) as a crude measure of adiposity (Morita *et al.*, 2011). Also, weight gain is associated with periodontal disease progression (Gorman *et al.*, 2012). If left untreated, periodontitis eventually leads to tooth loss, and increased tooth loss was shown to be associated with obesity (Nyholm *et al.*, 2009). Moreover, incident tooth loss is associated with socioeconomic factors that may also influence the risk of obesity.

There exists an apparent paradox to be resolved in that women are known to express higher levels of systemic CRP in relation to obesity (Thorand *et al.*,

2007), whereas they are periodontally healthier than men (Shiau and Reynolds, 2010). Thus, if the association of obesity with periodontitis and tooth loss is mediated by inflammation, then it must be differently regulated between men and women. The aim of this follow-up study was to evaluate potential sex differences in associations of adiposity and low-grade inflammation with tooth loss.

MATERIAL & METHODS

Study Design and Sample

The Study of Health in Pomerania (SHIP) is a longitudinal population-based health study of a 20- to 80-yr-old population in Germany. Approved by the local ethics committee, baseline study SHIP-0 is based on a representative age-stratified cluster sample examined from 1997 to 2001 in West Pomerania. Subjects were drawn at random from official resident data files proportional to the population size of each community and stratified by age and sex (Völzke *et al.*, 2011). Five years later, 3,300 subjects from SHIP-0 were again examined in SHIP-1 (response, 76.9%). For this study, participants edentulous at baseline and those with CRP levels > 10 mg/L were excluded. Finally, 2,746 subjects were included for the present analysis: 1,337 men and 1,409 women.

Dental Examination

Dental examinations were conducted in rotation by 5 trained, calibrated, and licensed dentists (Hensel *et al.*, 2003). Assessing the number of teeth included all teeth except the third molars (maximum, 28 teeth). Measurements of clinical attachment loss (CAL) were assessed with a periodontal probe (PCP 11, HuFriedy, Chicago, IL, USA) at distobuccal, midbuccal, mesio-buccal, and midlingual sites according to the half-mouth method, alternating on the left or the right side (maximum, 14 teeth). If recession was present at the examined site, attachment loss was directly measured as the distance between the cemento-enamel junction and the pocket base, rounded to whole millimeters. Dental caries was assessed as the number of prevalent filled and decayed teeth, dichotomized as being present or not (1/0). Visual inspection and probing determined the presence or absence of marginal plaque, presented as extent in percentage.

Independent Variables

Sociodemographic variables and periodontal risk factors were taken from interviews and questionnaires. Education level was divided according to the final school grade (< 10, 10, > 10 yr). Income was dichotomized at < 50% of average German income (< 960 euros). BMI (kg/m²) was categorized into 3 groups: ≥ 18.5 , < 25; ≥ 25 , < 30; and ≥ 30 . Waist-to-hip ratios (WHRs) were divided into tertiles specifically calculated for either sex and waist circumference into deciles for illustrative purposes.

For anthropometrics, all measurements were taken under standardized conditions according to a balance- and height-measuring device (Soehnle, Murrhardt, Germany). Body weight was measured to the nearest 0.10 kg on a decimal scale, height

to the nearest 1 cm, waist and hip circumferences to the nearest 0.5 cm. Waist girth was measured at the midpoint between the lower ribs and the iliac crest. Hip circumference was measured horizontally at the level of the largest lateral extension of the hips or over the buttocks. Smoking behavior, socioeconomic status, and data on oral hygiene were assessed with an extensive questionnaire and an interview.

A nonfasting blood sample was drawn from the antecubital vein in supine position and immediately analyzed or stored at -80°C . IL-6 was measured with a chemiluminescent immuno-metric assay (Siemens Immulite 2500, Siemens, Bad Nauheim, Germany). High-sensitivity CRP was determined in serum by particle-enhanced immunonephelometry (hsCRP kit, Dade Behring) with a test sensitivity of 0.2 mg/L. For dichotomization of CRP levels, a threshold of 2 mg/L was set. Serum IL-6 levels were dichotomized at 2.5 pg/mL.

Data Analysis

Tooth loss is the difference between the baseline number of teeth minus that at follow-up. Contingence tables and Mann-Whitney tests were used to assess differences and negative binomial regression to estimate the effects of anthropometric measures on tooth loss, adjusting for confounding variables. Follow-up time varied between 4.4 and 8.5 yr (mean, 5.26; 95% confidence interval: 5.24, 5.28). For this reason, the log-transformed follow-up time was included as an offset variable in all regression analyses. Analyses were performed with software STATA 10.0 (Stata Corp LP, College Station, TX, USA).

RESULTS

Table 1 provides descriptive statistics of the baseline data relevant to this study for each sex, stratified according to the obesity status. Marked sex differences were observed in all parameters listed, in anthropometric and dental measures, and in risk factors for tooth loss. In periodontitis, as characterized by CAL, risk factors, and tooth loss, a significantly better pattern was revealed in women as compared to men. Nevertheless, the number of teeth was not different between both sexes. Markers of systemic inflammation, circulating CRP concentration, and IL-6 levels were higher in women, especially in the obese ones.

The crude figures of tooth loss and CRP concentrations in relation to waist circumference are shown in Figure 1. With increasing waist circumference, the number of lost teeth increased; the relationship was more pronounced in men than in women. CRP levels were likewise related to waist but tended to be higher in women as compared to their male counterparts (see Table 1). These relationships were also observed as a dose-effect relationship with increasing tooth loss across the BMI or WHR categories (Table 2). Furthermore, increased levels of CRP or IL-6 were significantly associated with the risk of losing 1 or more teeth. Men with increased CRP had 50% higher odds to lose 1 or more teeth during the follow-up period as compared to men with CRP ≤ 2 mg/L (incidence rate ratio [IRR] = 1.50, $p < .001$). In women, this association was less distinctive (IRR = 1.18, $p = .026$). For increased concentrations of IL-6, similar relationships were observed with regard to tooth loss.

Table 1. Baseline Variables of Interest by Obesity and Sex

Variables	18.5 ≤ BMI < 30		BMI ≥ 30	
	Male(n = 1,011)	Female(n = 1,065)	Male(n = 324)	Female(n = 314)
Age, yr	47.9 ± 15.1	45.5 ± 14.2**	52.5 ± 13.1	52.5 ± 12.8
BMI, kg/m ²	25.9 ± 2.5	24.4 ± 2.9**	32.9 ± 2.8	33.8 ± 3.1**
Ratio				
Waist to hip	0.91 ± 0.06	0.79 ± 0.06**	0.98 ± 0.05	0.85 ± 0.06**
Waist to height	0.52 ± 0.05	0.47 ± 0.06**	0.62 ± 0.05	0.61 ± 0.06**
A1C				
%	5.4 ± 0.8	5.2 ± 0.7**	5.8 ± 1.1	5.6 ± 0.9*
> 6.5%	60 (5.9)	43 (4.0)*	49 (15.1)	34 (10.8)
Teeth (edentulous excluded)	20.4 ± 7.5	21.0 ± 6.7	19.3 ± 7.4	18.0 ± 8.0
Clinical attachment loss, mm	2.7 ± 1.9	2.2 ± 1.5**	3.4 ± 1.9	2.9 ± 1.7**
Extent probing depth ≥ 4 mm ^a	7.1 (0-19)	3.6 (0-12)**	11.5 (3-29)	6.6 (2-17)**
Dental plaque ^a	54.2 (29-81)	41.7 (21-70)**	70.8 (42-92)	56.3 (35-80)*
Dental visits				
Per year	2.5 ± 2.6	3.1 ± 3.1**	2.4 ± 2.8	2.8 ± 3.0*
Last > 1 yr	125 (12.3)	70 (6.4)**	44 (13.6)	26 (8.39)**
Poor dental hygiene	227 (22.5)	64 (6.0)**	108 (33.3)	37 (11.8)**
Caries lesions	227 (22.5)	217 (20.4)	92 (28.4)	70 (22.3)
C-reactive protein				
mg/L	1.7 ± 1.8	1.8 ± 2.0	2.3 ± 2.0	3.5 ± 2.6**
> 2 mg/L	252 (24.9)	302 (28.4)	125 (38.6)	195 (62.1)**
Interleukin 6, pg/mL	2.5 ± 2.2	2.4 ± 1.7*	2.8 ± 2.4	3.3 ± 9.2
Physical activity > 1 hr/wk	426 (42.1)	526 (49.4)**	126 (38.9)	125 (39.8)
Education < 10th grade	325 (32.1)	271 (25.4)**	146 (45.1)	143 (45.5)
Poverty ^b	533 (52.7)	606 (56.9)	152 (46.9)	196 (62.4)**
Current smokers	318 (31.5)	243 (22.8)**	67 (20.7)	57 (18.2)**

Values in mean ± SD or no. (%).

BMI, body mass index.

^aMedian (interquartile range). In percentages.

^bLess than 50% of average German income.

p* < .05. *p* < .01. Between males and females.

Figure 1. Left: Number of teeth lost during the 5-yr follow-up period by sex-specific deciles of waist circumference in men and women (for both, trend was *p* < .001). Right: C-reactive protein (CRP) serum concentrations in men and women by sex-specific waist circumference deciles (trend was *p* < .001 and *p* = .003 for men and women, respectively).

Table 2. Crude Association Between Any Tooth Loss and BMI or WHR Tertiles by Sex

	Males			Females		
	Tooth Loss ≥ 1	No Tooth Loss	IRR (95% CI)	Tooth Loss ≥ 1	No Tooth Loss	IRR (95% CI)
BMI, kg/m ²						
< 25	108	231	1	181	438	1
≥ 25 , < 30	282	390	1.34 (1.12, 1.60)**	173	273	1.34 (1.13, 1.59)**
≥ 30	149	175	1.47 (1.21, 1.79)**	124	190	1.36 (1.13, 1.63)**
WHR, tertile						
First	153	312	1	126	357	1
Second	212	299	1.28 (1.08, 1.51)**	185	336	1.37 (1.14, 1.66)**
Third	173	184	1.50 (1.27, 1.77)**	167	206	1.71 (1.42, 2.06)**
Plaque, tertile						
First	107	279	1	132	400	1
Second	149	277	1.20 (0.98, 1.47)	142	291	1.20 (0.99, 2.46)
Third	271	233	1.83 (1.54, 2.18)**	188	205	1.76 (1.48, 2.09)**
C-reactive protein, mg/L						
≤ 2.0	338	620	1	288	594	1
>2	201	176	1.50 (1.32, 1.71)**	190	307	1.18 (1.02, 1.37)*
Interleukin 6, μ g/L						
≤ 2.5	399	665	1	378	755	1
> 2.5	140	131	1.38 (1.20, 1.58)**	100	146	1.22 (1.03, 1.45)*

During 5 yr of follow-up. For comparison, categories of dental plaque, C-reactive protein, and interleukin 6 are included. Incidence rate ratios (IRRs) corrected for follow-up time.

BMI, body mass index; CI, confidence interval; WHR; waist-to-hip ratio.

* $p < .05$. ** $p < .01$.

Tooth loss was related to BMI after adjustment for age, socioeconomic factors, smoking, dental hygiene, and physical activity. Inclusion of frequency of dental attendance, self-report of mobile teeth at baseline, or caries did not attenuate the association. Inclusion of dental plaque or CRP attenuated the relationship between BMI or WHR and tooth loss in men but not women. Accordingly, effect modification was observed between sex and CRP ($p = .006$). Thus, we stratified the analyses according to sex, as shown in Table 3.

We observed distinct differences in obesity measures between men and women. The impact of elevated BMI on tooth loss was higher in men than in women, but the IRRs associated with the upper WHR tertiles were higher in women. Inclusion of CRP attenuated the IRR, an influence effective in men but not in their female counterparts. In women, the IRR with respect to CRP was negligible in comparison to that exerted by CRP in men. In contrast, inclusion of dental plaque was effective in both men and women. Severity of periodontitis as indicated by CAL is a measure of oral inflammatory burden. When these analyses were adjusted for mean CAL, the WHR-related IRR for incident tooth loss was abolished completely in men but only partially attenuated in women (not shown).

DISCUSSION

We observed an association between incident tooth loss during 5 yr and BMI and WHR. This association was modified by marked differences between the sexes and interference by inflammatory markers. Women were of better periodontal health but were burdened with higher levels of CRP than were their male counterparts. Yet, as compared with men, the modification

exerted by CRP on the association between obesity and tooth loss was much lower in women or even nil. Sex disparities were also obvious, as tooth loss was more strongly associated with WHR in women but with BMI in men. These relationships remained significant when regression analyses were adjusted for risk factors for tooth loss, such as smoking, socioeconomic factors, health behavior with respect to dental treatment, caries, and periodontal measures. Only local (plaque, CAL) or systemic (CRP, IL-6) measures of inflammation attenuated the association between tooth loss and anthropometric measures.

Attitudes toward and biology of oral health are very different between men and women, resulting in a dimorphism in susceptibility to periodontitis (Meisel *et al.*, 2008; Shiau and Reynolds, 2010; Russell *et al.*, 2013). Thus, the results give evidence of distinct responses between men and women in the metabolic pathways connecting obesity and tooth loss. Besides their impact on fat metabolism and fat distribution, protective effects of estrogens may be relevant to alveolar bone loss and tooth loss (Meisel *et al.*, 2008). In patients with periodontitis and concomitant postmenopausal osteoporosis, a lack of this hormone may be deleterious (Lerner, 2006). In the present study, postmenopausal women lost fewer teeth when treated with hormone replacement therapy as compared to those without (not shown). However, we could not find different responses in pre- and postmenopausal women with respect to the adiposity-related outcome as shown in Table 3.

Obesity is associated with elevated levels of CRP with marked sex differences, and fat distribution is more strongly associated with systemic CRP in women than in men (Linden *et al.*, 2008; Valentine *et al.*, 2009). Sex differences in the relationships between WHR and tooth loss suggest that CRP may be partially involved as a mediator between visceral fat and tooth

Table 3. Incidence of Tooth Loss Regressed on Body Mass Index or Waist-to-Hip Ratio Categories: Stratified by Sex

Independents ^a	Males		Females	
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Body mass index, kg/m ²				
< 25	1	1	1	1
≥ 25, < 30	1.17 (0.90, 1.54)	1.14 (0.87, 1.49)	1.18 (0.91, 1.53)	1.17 (0.90, 1.52)
≥ 30	1.53 (1.13, 2.07)**	1.34 (0.99, 1.81)	1.08 (0.81, 1.43)	0.96 (0.70, 1.31)
Plaque, 10% increase	—	1.12 (1.08, 1.16)**	—	1.10 (1.05, 1.14)**
C-reactive protein > 2 mg/L	—	1.30 (1.05, 1.63)*	—	0.98 (0.77, 1.25)
Waist-to-hip ratio, tertile				
First	1	1	1	1
Second	1.33 (1.03, 1.71)*	1.20 (0.94, 1.55)	1.46 (1.12, 1.90)**	1.46 (1.12, 1.91)**
Third	1.37 (1.04, 1.80)*	1.17 (0.89, 1.54)	1.53 (1.14, 2.05)**	1.48 (1.09, 2.00)**
Plaque, 10% increase	—	1.12 (1.08, 1.16)**	—	1.09 (1.05, 1.13)**
C-reactive protein > 2 mg/L	—	1.33 (1.07, 1.66)*	—	0.92 (0.73, 1.17)

IRR, incidence rate ratio; CI, confidence interval.

^aAdjusted for age, smoking (3 categories), education (3 categories), income (< 960 euros), physical activity, poor dental hygiene, caries (present or not), frequency of dental visits/year, mobile teeth at baseline (self-reported).

* $p < .05$. ** $p < .01$.

loss in men but not women (Table 3). The impact of CRP on tooth loss remained unaffected after inclusion of dental plaque in the analyses. Dental plaque significantly predicted the incidence of tooth loss but did not abolish the relationship between WHR and tooth loss in women. In men, adjusting for dental plaque resulted in decreased IRR, especially of the BMI-associated tooth loss; that is, the obesity-related IRR (BMI > 30 kg/m²) decreased from 1.53 (95% confidence interval: 1.13, 2.07) to 1.40 (95% confidence interval: 1.05, 1.90). However, no sex differences were observed in the relationship between WHR and dental plaque or CAL.

CRP predicted tooth loss in men, an effect negligible in women (Table 3). Different signaling pathways were proposed linking obesity, inflammation, and periodontitis with emphasis on the central role of cytokines such as IL-6 or TNF- α (Genco *et al.*, 2005; D'Aiuto and Suvan, 2012). Nevertheless, it remains unclear how to construct a possible causal pathway. Increasing CRP levels were observed in relation to more extensive fat depots as well as a consequence of periodontal inflammation. In both directions, causality was proved by interventional measures. Circulating CRP decreases by successful weight loss programs whereby the sex differences in CRP levels were also abolished (Yatsuya *et al.*, 2011). Periodontal treatment improving the oral inflammation is also associated with decreasing concentrations of circulating CRP (Shimada *et al.*, 2010; López *et al.*, 2012). Otherwise, weight gain has more harmful effects on systemic inflammation in women than in men with respect to CRP (Ahonen *et al.*, 2012).

CRP appears to be a mediator between obesity and tooth loss. CRP attenuated the association between obesity and tooth loss. Whereas we accept the view that cytokines produced by fat tissues and/or peripheral inflammation sites stimulate CRP formation, there is no rationale to take CRP or other acute phase proteins as mediators. The CRP plasma concentration is determined by the hepatic synthesis rate, which is accelerated rapidly after acute inflammatory stimuli (*e.g.*, IL-6) and is permanently raised in chronic states. Under such circumstances, CRP is a marker

common for tissues or processes releasing mediators that are able to stimulate the CRP output of the liver. Otherwise, it would be necessary to speculate whether CRP has an active role influencing the severity of periodontitis. Up to now, there is no evidence that CRP is a direct partaker in the pathogenesis of periodontitis.

BMI or WHR has a different impact between the sexes on CRP levels and probably also on inflammatory diseases (Chitsazi *et al.*, 2008). Higher CRP concentrations found in women appear to be due to their greater accumulation of subcutaneous fat than that observed in men. Central adiposity and visceral fat are closely related to systemic inflammation as characterized by increasing CRP levels (Cartier *et al.*, 2009). Obesity-related measures such as BMI or WHR may have different impact on inflammation in men or women (Khera *et al.*, 2009; Chaffee and Weston, 2010; Choi *et al.*, 2013). Whereas BMI allows a rather crude assessment of adiposity, WHR represents an appropriate measure related to fat distribution. Abdominal visceral adiposity was most consistently associated with significantly higher IL-6 and CRP concentrations, even after controlling for general adiposity (Beasley *et al.*, 2009). The question remains whether such sex-related differences are sufficient to explain different CRP levels and different susceptibilities to inflammatory diseases between men and women. A majority of studies support such assumptions, indicating that obesity-related measures such as BMI and WHR may have different impacts on inflammation in men and women (Khera *et al.*, 2009; Valentine *et al.*, 2009). Even so, these sex differences were not abolished after perfect matching for BMI between men and women (Rogowski *et al.*, 2004).

The data presented here may be important with respect to the well-documented associations of periodontitis, tooth loss, and obesity with systemic inflammatory diseases. Men carry a disproportionately stronger burden of these diseases. Tooth loss is related to subclinical atherosclerosis in men but not in women (Desvarieux *et al.*, 2004). The number of teeth also seems to be a predictor of mortality independent of health factors and socioeconomic status but with clear-cut sex differences (Osterberg *et al.*, 2008).

Our study has several limitations. First, we observed the incident tooth loss. However, the associations between obesity and CRP were cross-sectional with the baseline data preventing from drawing causal inferences about the relationship between obesity and CRP levels. Second, BMI and waist circumference are surrogate markers for adiposity, and CRP is only one measure of inflammation probably induced by obesity and periodontal inflammation as well. Finally, residual confounding may interfere from inflammatory conditions other than periodontitis. In an attempt to minimize this confounding, we excluded individuals with CRP levels > 10 mg/L.

In conclusion, this study suggests that both adiposity and subclinical inflammation affect tooth loss, with distinct differences between men and women. Obesity as a risk factor for tooth loss may be modified by systemic markers of inflammation such as CRP and IL-6 in men but not in women. Further studies are needed to elucidate potential pathogenetic pathways of this discrepancy between sexes and to evaluate whether CRP may be a mediator in the process or merely a marker or a bystander.

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