MRS. PAULA TEGELBERG (Orcid ID : 0000-0001-5259-1859)

Article type : Original Article Clinical Periodontology

Long-term metabolic syndrome is associated with periodontal pockets and alveolar bone loss

Tegelberg P[1], Tervonen T[1], Knuuttila M[2], Jokelainen J[3,4], Keinänen-Kiukaanniemi S[4,5,6], Auvinen J[4,6,7], Ylöstalo P[1,2]

[1] Research Unit of Oral Health Sciences, Faculty of Medicine, University of Oulu, Oulu, Finland.

[2] Department of Oral and Maxillofacial Surgery, Oulu University Hospital, Oulu, Finland

[3] Center for Life Course Epidemiology and Systems Medicine, University of Oulu and Unit of Primary Care, Oulu, Finland

[4] Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland

[5] Healthcare and Social Services of Selänne, Pyhäjärvi, Finland

[6] Center for Life Course Health Research, Faculty of Medicine,University of Oulu, Health Center of Oulu, Oulu, Finland

[7] Oulunkaari Health Center, Ii, Finland

Running title: Metabolic syndrome and periodontal infection

Key words: Cohort study; periodontitis; periodontal infection; metabolic syndrome

Address:

Paula Tegelberg

Research Unit of Oral Health Sciences

University of Oulu

PO Box 5000

90014 University of Oulu, Oulu, Finland

E-mail: paula.tegelberg@oulu.fi

Statement of sources of funding for the study: The first author was financially supported by the Finnish Dental Society Apollonia and the Finnish Women Dentists' Association.

Conflict of Interest: The authors declare no conflicts of interest.

Abstract

Aim: To investigate whether the metabolic syndrome (MetS) is associated with deepened periodontal pockets and alveolar bone loss.

Materials and methods: This study was based on a subpopulation of the Northern Finland Birth Cohort 1966 survey (*n* = 1964). The criteria of the AHA/NHLBI were used to determine MetS. The analyses were based on the metabolic data at ages 31 and 46, and probing pocket depth and alveolar bone level data at age 46. Relative risks (RR, 95% CI) were estimated using Poisson regression models.

Results: RRs for PD ≥ 4 mm and BL ≥ 5 mm were higher in individuals with an exposure to MetS ≥ 15 years (RR 1.8, 95% CI 1.6–2.1 and RR 1.5, 95% CI 1.3–1.9, respectively) than in those whose exposure was < 15 years (RR 1.2, 95% CI 1.1–1.3 and RR 1.1, 95% CI 1.0–1.3, respectively). Consistently stronger associations were found in never-smokers. Females showed stronger associations of MetS with PD ≥ 4 mm than males. The association with BL ≥ 5 mm was observed only in males.

Conclusion: A long-term exposure by MetS was associated independently and in an exposure–dependent manner with periodontal pockets and alveolar bone level.

Clinical Relevance:

Scientific rationale for the study: Metabolic syndrome (MetS) has been found to be associated with periodontitis in a number of cross-sectional studies. The aim was to study whether a long-term metabolic syndrome is associated with periodontal disease parameters such as pocketing and bone loss.

Principal findings: The long-term metabolic syndrome was associated with periodontal pockets and alveolar bone loss in an exposure dependent manner.

Practical implications: MetS was found to be related to a high number of sites with deepened periodontal pockets and bone loss. Patients diagnosed with MetS have a higher risk of ~~developing~~ periodontitis.

Individuals with MetS have an increased risk for periodontitis.

Introduction

Metabolic syndrome (MetS) consists of a group of metabolic conditions including central obesity, insulin resistance and associated glucose imbalance, dyslipidemia and hypertension. It has been defined using different criteria and commonly used definitions include those set by the International Diabetes Federation (IDF) (Alberti et al. 2005), the American Heart Association / National Heart, Lung and Blood Institute (AHA/NHLBI) (Grundy 2005, Grundy et al. 2005), the World Health Organization (WHO) (Alberti & Zimmet 1998) and the National Cholesterol Education Panel (NCEP) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2002).

As the prevalence of MetS varies by age, gender, ethnicity and race and, importantly, the criteria of MetS, its true prevalence is hard to determine. It has been reported to affect 10 to 84% of the population worldwide and around 25% of the population in developed countries (Kaur 2014, Misra & Khurana 2008, O'Neill & O'Driscoll 2015).

Like MetS, periodontitis is a highly prevalent disease. While the prevalence of moderate periodontitis ranges from 23% to 46% in Germany, Australia and the United States (Demmer & Papapanou 2010) (Eke et al. 2015), the overall proportion of individuals with severe disease forms varies between 10% and 20% (Demmer & Papapanou 2010, Kassebaum et al. 2014).

A vast majority of earlier studies approached the association between MetS and periodontitis using a cross-sectional study design with either MetS or periodontitis as the outcome. In many cases, those studies reported statistically significant associations between the two conditions (Lamster & Pagan 2017, Nibali et al. 2013, Watanabe & Cho 2014). A self-evident shortcoming of these cross-sectional studies is that they do not allow interpretations of causality between MetS and periodontitis.

To our knowledge, only a few longitudinal studies have shown that a long-term metabolic syndrome predisposes to the progression of periodontitis (Iwasaki et al. 2015, Kaye et al. 2016) and to tooth loss (Furuta et al. 2016). None of the above longitudinal studies addressed possible gender differences in the studied associations.

In light of the overall high prevalence of both MetS and periodontitis, it is important to study whether MetS is a risk factor for periodontitis. To this end, longitudinal studies are obviously needed. The aim in our study was therefore to investigate whether MetS is related to periodontal parameters such as periodontal pockets and alveolar bone loss.

Materials and methods

The Northern Finland Birth Cohort 1966 (NFBC1966) is a life-span cohort study of health and well-being of individuals born in 1966 in the two northernmost provinces in Finland (Oulu and Lapland). In 2012–2013, when the subjects were 46-year-olds, an oral health examination was conducted for the first time on 1,964 participants living in the city of Oulu or within a 100 km radius of Oulu, the largest city in the area. The data used in this study included periodontal data from the 46-year follow-up examination and the metabolic data from the examinations at ages 31 and 46. Subjects with rheumatic and inflammatory intestinal and lung diseases were excluded; these diagnoses were obtained from the registries of the National Institute for Health and Welfare (THL). The study was approved by the Ethical Committee of the Hospital District of Northern Ostrobothnia.

Periodontal variables

Periodontal data, including dental plaque, probing pocket depth (PD) and bleeding on probing (BOP) from all teeth excluding third molars and residual roots were collected by seven calibrated dentists using a mouth mirror and a ball pointed periodontal probe with 2 mm grading (LM 8-520B, Lääkintämuovi, Finland).

The presence of plaque was examined from buccal sites and categorized as follows: 1 = no plaque, 2 = visible plaque or plaque, as measured by touching tooth site lightly with the periodontal probe. The number of teeth with dental plaque (continuous variable) was used in the statistical analyses.

Probing pocket depths were measured at four sites per tooth (mesiobuccal, midbuccal, distobuccal, midoral). Probing force (25 g) was calibrated using a letter scale before examining each participant. The number of sites with ≥ 4 mm probing depth (PD ≥ 4 mm), was used both as a continuous and as a categorized (0, 1–3, 4–7 and ≥ 8 sites) variable. The inter- and intra-examiner agreements for PD measurements were 70% and 82% and the Cohen's kappa values were 0.35 and 0.50, respectively.

Bleeding on periodontal probing (BOP) at the four sites was registered and, in the analyses, the variable was employed as percentages of bleeding sites.

Alveolar bone level (BL) on approximal sites of all teeth was measured from panoramic radiographs by one dental hygienist and one dentist. Panoramic radiographs were available of 1,584 subjects. The distance from the cemento-enamel junction (CEJ) to the most coronal point where the

periodontal ligament space still remained at its normal width was measured in millimeters. Any sites where the CEJ or the alveolar crest could not be identified were excluded. The number of sites with ≥ 5 mm BL was used both as a continuous and as a categorized (0, 1–3, 4–7 and ≥ 8 sites) variable. The inter- and intra-examiner agreements for BL measurements were 68% and 70% and the Cohen's kappa values were 0.54 and 0.59 respectively.

Metabolic syndrome

The metabolic syndrome at ages 31 and 46 was defined by the AHA/NHLBI (Grundy 2005, Grundy et al. 2005) criteria as follows:

a) elevated waist circumference (≥ 102 cm in males, ≥ 88 cm in females),

b) elevated triglycerides (≥ 1.7 mmol/l or on drug treatment),

c) reduced HDL cholesterol (< 0.9 mmol/l in males, < 1.1 in females or on drug treatment),

d) elevated blood pressure (≥ 130 mmHg / ≥ 85 mmHg or on drug treatment), and

e) elevated fasting glucose (≥ 100 mg/dl or on drug treatment).

As any combination of at least three of these five components constitutes the definition of metabolic syndrome (Grundy 2005, Grundy et al. 2005)**,** the components were categorized into two categories: less than three components versus three or over. Information for defining the MetS components was obtained in clinical and laboratory examinations. Drug treatment data were obtained by means of a questionnaire.

Other variables

The data on socio-demographics and health behavior were based on a questionnaire (Tables 1-3). With the exception of smoking history, the data were based on the examination made at age 46. Education was categorized into three categories: basic (no upper secondary school or vocational education), intermediate (graduated from upper secondary school or vocational school) and higher (graduated from university or university of applied sciences). The frequency of physical exercise was divided into four categories: 2–3 times a month or less frequently, once a week, 2–3 times a week and daily or 4–6 times a week. Alcohol consumption (g/day) was categorized as follows: abstainers (0 g/day) and tertiles of alcohol users (< 3.0 g/day, 3.0–11.1 g/day and > 11.1 g/day). Toothbrushing frequency was divided into three categories: twice a day or more frequently, once a day, and less frequently. Information on the most recent dental visit was divided into three categories: less than 1 year ago, 1–2 years ago and ≥3 years ago. Smoking history, based on the questionnaire data at ages 31 and 46, was divided into three categories: never-smokers, former smokers and current smokers.

Statistical analyses

The associations of MetS with the numbers of sites with PD ≥ 4 mm and BL ≥ 5 mm were investigated using the periodontal data of the examination at age 46 and metabolic data as follows: (i) metabolic status at the age of 31, (ii) long-term metabolic status between ages 31 and 46: < 15 where MetS manifested itself between ages 31 and 46 and ≥ 15 years where MetS was manifest at both ages, and (iii) metabolic status at the age of 46 (Table 5).

The long-term metabolic status could be defined for 1496 subjects. MetS never affected 1,102 individuals (62%) and manifested itself in 243 individuals (14%) between ages 31 and 46 (duration < 15 years). A reversal from MetS to normal metabolic status occurred in 60 individuals (3%) and MetS was manifest in 91 individuals (5%) at both ages (duration ≥ 15 years) (Table 3).

In the analyses, the numbers of sites with PD ≥ 4 mm and BL ≥ 5 mm at the age of 46 were used as continuous outcome variables and the metabolic status as the explanatory variable. Relative risks (RR) and 95% confidence intervals (95% CI) were estimated using Poisson regression models (Table 5). Smoking history, gender, dental visits, education and plaque, all associated with both the outcome and the main explanatory variable, were used as covariates; plaque as a continuous and the others as categorized variables. The number of sites (continuous variable) was used as an offset variable. The analyses were carried out among male, female and never-smokers. The statistical analyses were done using the IBM SPSS statistical software, version 22.

Results

Characteristics of subjects

Participants with high numbers of sites with PD ≥ 4 mm and BL ≥ 5 mm were more often males, less educated, current smokers and had poor health habits (Tables 1 and 2). MetS was more common in less educated subjects, participants with poor health habits and individuals with a poor periodontal conditions (Table 3). In both genders, the prevalence of MetS increased between ages 31 and 46: in men from 14.1% to 28.9% and in women from 6.7% to 16.5% (Table 4). With the exception of the weight variables, increased waist circumference and BMI ≥ 30, and low HDL at age 31 years, all components of MetS occurred more frequently in men than in women at both ages (Table 4). The mean number of teeth (third molars excluded) was 26.7 for individuals without MetS, 26.6 for those whit MetS < 15 years and 26.1 for those with MetS ≥ 15 years (Table 3).

Results of the regression models

The results of the regression models are presented in Table 5. MetS at the age of 31 was associated with PD ≥ 4 mm but not with BL ≥ 5 mm. The association with PD ≥ 4 mm was strongest in the sub-group of never-smokers (RR 1.4, 95% CI 1.2–1.7).

MetS < 15 years was only weakly associated with the number of sites with PD ≥ 4 mm. The strongest associations of MetS with PD ≥ 4 mm and BL ≥ 5 mm were found in cases where the metabolic syndrome had been manifest for ≥ 15 years. In these cases, the relative risk for PD ≥ 4 mm was 1.8 (95% CI 1.6–2.1) and for BL ≥ 5 mm 1.5 (95% CI 1.3–1.9) in the total population. Never-smokers presented consistently stronger associations between MetS and both PD ≥ 4 mm and BL ≥ 5 mm when compared with the total population. In the stratified analysis according to gender, it was observed that MetS ≥ 15 years was associated with PD ≥ 4 mm both in males (RR 1.6, 95% CI 1.4–1.9) and in females (RR 2.8, 95% CI 2.2–3.4). The association with BL ≥ 5 mm was observed only in males (RR 1.7, 95% CI 1.4–2.1).

MetS at the age of 46, was associated with the number of sites with PD ≥ 4 mm in the total population (RR 1.3, 95% CI 1.2–1.4). The associations were stronger in the subgroups of never-smokers (RR 1.7, 95% CI 1.5–1.9) and females (RR 1.7, 95% CI 1.5–1.9). The association of MetS with BL ≥ 5 mm was consistently weaker than with PD ≥ 4 mm.

In order to explore the effect of health habits not included in the above analyses, alcohol consumption, toothbrushing frequency and physical activity were separately added into the regression models. This had no essential effect on the risk estimates; with the exception of RR for PD ≥ 4 mm in females at the age of 31, which decreased by 0.5, risk estimates did not change more than 0.2.

Discussion

This study provided evidence that MetS is associated with the extent of periodontal pocketing and alveolar bone loss in an exposure dependent manner. This association was stronger among never smokers than in the total study population.

In terms of the long-term effects of MetS on the periodontium, our findings are in line with earlier longitudinal studies. A study among older Japanese adults reported that MetS was associated with the development of periodontal disease defined as loss of attachment of ≥ 3 mm in ≥ 2 teeth over a 3-year period (RR 2.67, 95% CI 1.1–6.5) (Iwasaki et al. 2015). Another Japanese study reported that, compared with metabolically healthy individuals, those with ≥ 3 metabolic components were 50% more likely to lose teeth during a 5-year period (OR 1.54, 95% CI 1.0–2.4) (Furuta et al. 2016). To study whether MetS is a risk factor for periodontal disease, Kaye and his group (Kaye et al. 2016) followed a cohort of 720 men for a mean follow-up period of 17 years and found out that MetS predicted greater risks of tooth loss and the development or worsening of periodontitis. In addition, supporting the conclusion that individuals with signs of metabolic syndrome at a young age might have a high risk for periodontitis as adults (Lee et al. 2015), we found that MetS at the age of 31 associated with the presence of PD ≥ 4 mm 15 years later.

The exposure–dependent association between MetS and the extent of pocketing and alveolar bone level lends supports to a view that MetS could be causally related to periodontal condition; a conclusion that fits well to the prevailing conception that a low-grade systemic inflammation mediates the association of MetS with periodontium. Systemic inflammation has, indeed, been associated with MetS as a composite condition and with its individual components (Haffner 2003, Kirilmaz et al. 2010, Yudkin et al. 2004) and – in 'a consistent and dose–dependent manner' – with periodontitis (Pink et al. 2015). As to the biological pathways between the low-grade systemic inflammation and periodontitis, the detrimental effects of pro-inflammatory cytokines (Graves 2008, Passoja et al. 2011, Saxlin et al. 2009) and oxidative stress (Bullon et al. 2009) on periodontal tissues are well known. Our study showed associations specifically between long-term MetS (≥ 15 years) and BL ≥ 5 mm, a long-term measure of periodontal infection, suggesting that MetS could be a predisposing factor to alveolar bone loss.

Several cross-sectional studies have reported stronger associations of MetS with periodontal pocketing (PD ≥ 4) mm in females than males (Andriankaja et al. 2010, Furuta et al. 2013, Kwon et al. 2011, Tu et al. 2013), but so far no data exist of possible gender differences in the response of periodontal tissues to long-term metabolic burden. At ages 31 and 46, MetS was almost twice as prevalent in males than in females. Due to longer exposure by MetS in males, we expected gender differences and therefore stratified the sample by gender. Another explanation for the differences between genders could relate to life-style or health habits, which mask the true association of MetS with periodontal pocketing. Speculations on other reasons, such as a higher level of systemic inflammation due to abdominal obesity in females or the role of oestrogen in the inflammatory process have been previously presented by other authors (Andriankaja et al. 2010, Kwon et al. 2011).

To control for confounding in the studied associations we adjusted for potential confounding factors. Of the potential confounders, gender, smoking, education and dental visits were common denominators in common for MetS and the outcome variables. Regrettably we had no suitable data to study whether periodontal treatment had any effect on the studied associations. The previous means that we cannot definitely exclude the possibility of bias due to residual confounding. To avoid biases due to smoking (Hujoel et al. 2002), we also performed analyses among non-smokers. These analyses showed consistently stronger associations than in the total population, which supports the interpretation that the association is not a result of confounding due to smoking. Finally, in terms of confounding, the complexity of the relation between MetS and periodontitis should be kept in mind. Here we are making reference to 'a vicious circle' in which periodontal infection itself increases the risk for MetS (Morita et al. 2010).

Our study includes several strengths; one of them is the life-long NFBC1966 survey data, which made it possible for us to determine the long-term exposure of MetS. Importantly, the prevalence of MetS in the present study population was close to the levels reported in earlier national studies in Finland (Hu et al. 2008, Ilanne-Parikka et al. 2004). The accuracy of the clinical data is supported by the fact

that the strength of the association between MetS and periodontal infection at the age of 46 was on the level reported in earlier studies (Furuta et al. 2013, Kwon et al. 2011, Tu et al. 2013).

Another strength was that we could use a long-term measure of periodontal infection (BL ≥ 5 mm) and relate it to the long-term exposure by MetS. From the methodological point of view, it was salient that the number of teeth at risk of periodontal infection was quite high and, notably, similar in individuals with and without MetS. This means that selective tooth loss may not have any essential effect on the results. Another methodological point was that we took into account possible systemic inflammation due to reasons other than MetS by excluding individuals with systemic inflammatory diseases. Lastly, we used continuous outcome variables (numbers of sites with PD ≥ 4 mm and BL ≥ 5 mm) in the regression analyses to reduce misclassification of periodontal infection (Kwon et al. 2011).

In the context of this study, we focused on MetS as one condition and defined its long-term duration based on the presence of any three of its components at ages 31 and 46. One shortcoming in this study was that we could not determine the time of exposure by MetS more precisely. In our approach, an exposure of < 15 years meant that the conversion from a normal metabolic state to MetS occurred at an unknown point in time between the ages 31 and 46. Also, regarding the exposure of ≥ 15 years, we do not know, how long it took before the age of 31 that MetS manifested itself. The lack of periodontal follow-up data is due to the fact that the oral examination was included in the NFBC survey protocol for the first time when the cohort was 46 years old. This naturally prevented us from determining the effect of MetS on the true incidence of pocket formation and alveolar bone loss. Another shortcoming was the overall poor reproducibility of the periodontal and radiological data, which was no higher than moderate. The effect of the poor reproducibility is most likely towards zero, *i.e.* attenuating the observed association.

To summarize, long-term exposure by MetS was associated independently and in an exposure–dependent manner with periodontal disease parameters such as periodontal pockets and alveolar bone level.

References

Alberti KG, Zimmet P & Shaw J (2005) The metabolic syndrome – a new worldwide definition. Lancet 366: 1059-1062. doi: 10.1016/S0140-6736(05)67402-8.

Alberti KG & Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic Medicine 15: 539-553. doi: 10.1002/(SICI)1096-9136(199807)15:73.0.CO;2-S.

Andriankaja OM, Sreenivasa S, Dunford R & DeNardin E (2010) Association between metabolic syndrome and periodontal disease. Australian Dental Journal 55: 252-259. doi: 10.1111/j.1834-7819.2010.01231.x.

Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN & Battino M (2009) Metabolic syndrome and periodontitis: is oxidative stress a common link? Journal of Dental Research 88: 503-518. doi: 10.1177/0022034509337479.

Demmer RT & Papapanou PN (2010) Epidemiologic patterns of chronic and aggressive periodontitis. Periodontol 2000 53: 28-44. doi: 10.1111/j.1600-0757.2009.00326.x.

Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, Taylor GW, Page RC, Beck JD & Genco RJ (2015) Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. Journal of Periodontology 86: 611-622. doi: 10.1902/jop.2015.140520.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2002) Third Report of the National Cholesterol Education Program (NCEP) (Adult Treatment Panel III) final report. Circulation 106: 3143-3421.

Furuta M, Liu A, Shinagawa T, Takeuchi K, Takeshita T, Shimazaki Y & Yamashita Y (2016) Tooth loss and metabolic syndrome in middle-aged Japanese adults. Journal of Clinical Periodontology 43: 482-491. doi: 10.1111/jcpe.12523.

Furuta M, Shimazaki Y, Takeshita T, Shibata Y, Akifusa S, Eshima N, Kiyohara Y, Ninomiya T, Hirakawa Y, Mukai N, Nagata M & Yamashita Y (2013) Gender differences in the association between metabolic syndrome and periodontal disease: the Hisayama Study. Journal of Clinical Periodontology 40: 743-752. doi: 10.1111/jcpe.12119.

Graves D (2008) Cytokines that promote periodontal tissue destruction. Journal of Periodontology 79: 1585-1591. doi: 10.1902/jop.2008.080183.

Grundy SM (2005) Metabolic Syndrome Scientific Statement by the American Heart Association and the National Heart, Lung, and Blood Institute. Arteriosclerosis, Thrombosis, and Vascular Biology 25: 2243-2244. doi: 0.1161/01.ATV.0000189155.75833.c7.

Grundy SM, Cleeman JI, Danielas SR, Donate KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F (2005) Diagnosis and management of the metabolic syndrome, an American Heart Association/National Heart, Lung, and Blood Institute, Scientific Stament. Circulation, 112: 2735-2752. doi: 10.1161/CIRCULATIONAHA.105.169404.

Haffner SM (2003) Insulin resistance, inflammation, and the prediabetic state. The American Journal of Cardiology 92: 18-26. doi: 10.1016/S0002-9149(03)00612-X.

Hu G, Lindström J, Jousilahti P, Peltonen M, Sjöberg L, Kaaja R, Sundvall J & Tuomilehto J (2008) The Increasing Prevalence of Metabolic Syndrome among Finnish Men and Women over a Decade. Clin Endocrinol Metab 93(3): 832-836.

Hujoel PP, Drangsholt M, Spiekerman C & DeRouen TA (2002) Periodontitis-systemic disease associations in the presence of smoking--causal or coincidental? Periodontology 2000 31: 51-60.

Ilanne-Parikka P, Eriksson JG, Lindström J, Hämäläinen H, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Rastas M, Salminen V, Aunola S, Sundvall J, Valle T, Lahtela J, Uusitupa M & Tuomilehto J (2004) Prevalence of the metabolic syndrome and its components: findings from a Finnish general population sample and the Diabetes Prevention Study cohort. Diabetes Care 27: 2135-2140. doi: 10.2337/diacare.27.9.2135.

Iwasaki M, Sato M, Minagawa K, Manz MC, Yoshihara A & Miyazaki H (2015) Longitudinal relationship between metabolic syndrome and periodontal disease among Japanese adults aged ≥70 years: the Niigata Study. Journal of Periodontology 86: 491-498. doi: 10.1902/jop.2015.140398.

Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ & Marcenes W (2014) Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. Journal of Dental Research 93: 1045-1053. doi: 10.1177/0022034514552491.

Kaur J (2014) A comprehensive review on metabolic syndrome. Cardiology Reseach and Practise doi: 10.1155/2014/943162.

Kaye EK, Chen N, Cabral HJ, Vokonas P & Garcia RI (2016) Metabolic Syndrome and Periodontal Disease Progression in Men. Journal of Dental Research 95: 822-828. doi: 10.1177/0022034516641053.

Kirilmaz B, Asgun F, Alioglu E, Ercan E, Tengiz I, Turk U, Saygi S & Ozerkan F (2010) High inflammatory activity related to the number of metabolic syndrome components. Journal of Clinical Hypertension 1: 136-144. doi: 10.1111/j.1751-7176.2009.00229.x.

Kwon YE, Ha JE, Paik DI, Jin BH & Bae KH (2011) The relationship between periodontitis and metabolic syndrome among a Korean nationally representative sample of adults. Journal of Clinical Periodontology 38: 781-786. doi: 10.1111/j.1600-051X.2011.01756.x.

Lamster I & Pagan MM (2017) Periodontal disease and the metabolic syndrome. International Dental Journal 67: 67-77. doi: 10.1111/idj.12264.

Lee KS, Lee SG, Kim EK, Jin HJ, Im SU, Lee HK, Merchant AT, Song KB & Choi YH (2015) Metabolic syndrome parameters in adolescents may be determinants for the future periodontal diseases. Journal of Clinical Periodontology 42: 105-112. doi: 10.1111/jcpe.12338.

Misra A & Khurana L (2008) Obesity and the metabolic syndrome in developing countries. The Journal of Clinicial Endocrinology and Metabolism 93: 9-30. doi: 10.1210/jc.2008-1595.

Morita T, Yamazaki Y, Mita A, Takada K, Seto M, Nishinoue N, Sasaki Y, Motohashi M & Maeno M (2010) A cohort study on the association between periodontal disease and the development of metabolic syndrome. Journal of Periodontology 81: 512-519. doi: 10.1902/jop.2010.090594.

Nibali L, Tatarakis N, Needleman I, Tu YK, D'Aiuto F, Rizzo M & Donos N (2013) Association between metabolic syndrome and periodontitis: A systematic review and meta-analysis. The Journal of Clinicial Endocrinology and Metabolism 98: 913-920. doi: 10.1210/jc.2012-3552.

O'Neill S & O'Driscoll L (2015) Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obesity Reviews 16: 1-12. doi: 10.1111/obr.12229.

Passoja A, Knuuttila M, Hiltunen L, Karttunen R, Niemelä O, Raunio T, Vainio O, Hedberg P & Tervonen T (2011) Serum interleukin-6 may modulate periodontal inflammation in type 1 diabetic subjects. Journal of Clinical Periodontology 38: 687-693. doi: 10.1111/j.1600-051X.2011.01731.x.

Pink C, Kocher T, Meisel P, Dörr M, Markus MR, Jablonowski L, Grotevendt A, Nauck M & Holtfreter B (2015) Longitudinal effects of systemic inflammation markers on periodontitis. Journal of Clinical Periodontology 42: 988-997. doi: 10.1111/jcpe.12473.

Saxlin T, Suominen-Taipale L, Leiviskä J, Jula A, Knuuttila M & Ylöstalo P (2009) Role of serum cytokines tumour necrosis factor-alpha and interleukin-6 in the association between body weight and periodontal infection. Journal of Clinical Periodontology 36: 100-105. doi: 10.1111/j.1600-051X.2008.01350.x.

Tu YK, D'Aiuto F, Lin HJ, Chen YW & Chien KL (2013) Relationship between metabolic syndrome and diagnoses of periodontal diseases among participants in a large Taiwanese cohort. Journal of Clinical Periodontology (40): 994-1000. doi: 10.1111/jcpe.12157.

Watanabe K & Cho YD (2014) Periodontal disease and metabolic syndrome: A qualitative critical review of their association. Archives of Oral Biology 59: 855-870. doi: 10.1016/j.archoralbio.2014.05.003.

Yudkin JS, Juhan-Vague I, Hawe E, Humphries SE, di Minno G, Margaglione M, Tremoli E, Kooistra T, Morange PE, Lundman P, Mohamed-Ali V & Hamsten A (2004) Low-grade inflammation may

play a role in the etiology of the metabolic syndrome in patients with coronary heart disease: the HIFMECH study. Metabolism 53: 852-857. doi: 10.1016/j.metabol.2004.02.004.

Acknowledgements: The authors thank the late professor Paula Rantakallio for launching NFBC 1966, participants of the NFBC1966 46 years follow-up study and the NFBC project center. The first author thanks the Finnish Dental Society and the Finnish Women Dentists' Association for their financial support.

Table 1. Basic characteristics of the study population; proportions/means and their standard deviations (SD) in the categories of sites with ≥ 4 mm periodontal pockets (PD)

	Number of sites with PD ≥ 4 mm			
	0 (*n* = 882)	1–3 (*n* = 507)	4–7 (*n* = 173)	≥ 8 (*n* = 192)
Gender, % (*n* = 1754)				
Males	40.5	50.5	53.2	62.0
Education, % (*n* = 1652)				
Basic	31.7	41.4	47.2	62.2
Intermediate	46.4	41.0	39.8	31.7
Higher	21.8	17.5	13.0	6.1
Number of teeth mean (SD) (*n* = 1754)	26.8 (1.9)	26.6 (1.9)	26.6 (2.3)	26.2 (2.6)
Number of teeth with plaque, mean (SD) (*n* = 1754)	5.3 (6.0)	6.4 (6.3)	7.8 (7.0)	9.8 (7.8)
Smoking history, % (*n* = 1691)				
Never smokers	60.4	56.5	39.9	31.7
Former smokers	24.4	25.6	28.2	29.0
Current smokers	15.2	17.9	31.9	39.3
Toothbrushing frequency, % (*n* = 1702)				
Twice a day or more	72.3	65.1	62.2	50.8
Once a day	25.6	33.3	36.0	42.1
Less frequently	2.1	1.6	1.8	7.1
Most recent dental visit, % (*n* = 1704)				
Less than 1 year ago	59.6	57.9	55.4	46.7
1–2 years ago	28.2	27.2	22.6	28.8
≥ 3 years ago	12.2	14.9	22.0	24.5
Frequency of physical exercise, % (*n* = 1679)				
2–3 times a month or less frequently	23.1	26.3	29.8	34.8
Once a week	21.0	21.0	21.7	21.0
2–3 times a week	37.6	37.9	32.9	29.8
Daily or 4–6 times a week	18.2	14.8	15.5	14.4
Alcohol consumption, % (n = 1703)				
0 g / day	11.0	11.1	7.3	7.7
< 3.0 g / day	31.4	31.8	25.0	25.1
≥ 3.0–11.1 g /day	30.5	28.5	26.2	30.1
> 11.1 g / day	27.0	28.5	41.5	37.2
MetS, % (*n* = 1465)				
No Mets at 31 yrs / no MetS at 46 yrs	76.0	73.6	66.7	67.7
No MetS at 31 yrs / MetS at 46 yrs	15.5	16.0	17.7	20.5
MetS at 31 yrs / no Mets at 46 yrs	3.9	4.5	5.7	1.9
MetS at 31 yrs / MetS at 46 yrs	4.6	6.0	9.9	9.9
Prevalence of MetS at 31 yrs, % (*n* = 1465)	8.5	10.5	15.6	11.8
Prevalence of MetS at 46 yrs, % (*n* = 1754)	19.8	21.3	28.9	30.7

MetS, metabolic syndrome.

Table 2. Basic characteristics of the study population; proportions/means and their standard deviations (SD) in the categories of sites with ≥ 5 mm alveolar bone level (BL)

	Number of sites with BL ≥ 5 mm			
	0 (*n* = 778)	1–3 (*n* = 671)	4–7 (*n* = 106)	≥ 8 (*n* = 29)
Gender, % (*n* = 1584)				
Males	43.6	50.8	59.4	69.0
Education, % (*n* = 1493)				
Basic	35.7	42.1	44.4	60.7
Intermediate	42.7	43.5	44.4	28.6
Higher	21.7	14.4	11.1	10.7
Number of teeth, mean (SD) (*n* = 1571)	26.8 (1.8)	26.6 (2.2)	26.5 (1.9)	25.6 (2.4)
Number of teeth with plaque, mean (SD) (*n* = 1562)	5.9 (6.5)	6.5 (6.5)	6.8 (6.6)	6.1 (5.8)
Smoking history, % (*n* = 1526)				
Never smokers	60.8	49.9	42.6	22.2
Former smokers	23.0	28.0	27.7	18.5
Current smokers	16.2	22.1	29.7	59.3
Toothbrushing frequency, % (*n* = 1538)				
Twice a day or more	68.5	66.7	64.0	60.7
Once a day	29.4	30.7	33.0	25.0
Less frequently	2.1	2.6	3.0	14.3
Most recent dental visit, % (*n* = 1535)				
Less than 1 year ago	60.1	52.2	63.5	64.3
1–2 years ago	27.0	29.2	23.1	17.9
≥ 3 years ago	12.9	18.6	13.5	17.9
Frequency of physical exercise, % (*n* = 1518)				
2–3 times a month or less frequently	25.6	26.5	31.3	44.4
Once a week	20.5	21.7	17.2	22.2
2–3 times a week	36.4	36.3	32.3	22.2
Daily or 4–6 times a week	17.5	15.6	19.2	11.1
Alcohol consumption, % (n = 1539)				
0 g / day	12.0	10.3	5.0	0.0
< 3.0 g / day	30.7	29.9	26.7	21.4
≥ 3.0–11.1 g /day	30.9	28.2	27.7	14.3
> 11.1 g / day	26.4	31.6	40.6	64.3
MetS, % (*n* = 1316)				
No Mets at 31 yrs / no MetS at 46 yrs	72.8	75.0	69.6	60.0
No MetS at 31 yrs / MetS at 46 yrs	17.0	14.6	17.4	28.0
MetS at 31 yrs / no Mets at 46 yrs	4.3	4.5	2.2	0.0
MetS at 31 yrs / MetS at 46 yrs	5.9	5.8	10.9	12.0
Prevalence of MetS at 31 yrs, % (*n* = 1316)	10.2	10.3	13.0	12.0
Prevalence of MetS at 46 yrs, % (*n* = 1584)	23.5	20.0	29.2	34.5

MetS, metabolic syndrome.

Table 3. Basic characteristics of the study population; proportions/means and their standard deviations (SD) in subjects with no metabolic syndrome (MetS), with MetS < 15 years and with MetS ≥ 15 years

	No Mets (*n* = 1102)	MetS < 15 years (*n* = 243)	MetS ≥ 15 years (*n* = 91)
Gender, %			
Males	40.8	58.8	64.8
Education, %			
Basic	36.1	48.1	48.8
Intermediate	44.4	39.8	42.9
Higher	19.5	12.1	8.3
Smoking history, %			
Never smokers	58.4	43.8	49.2
Former smokers	24.1	32.3	28.8
Current smokers	17.5	23.8	22.0
Toothbrushing frequency, %			
Twice a day or more	70.8	62.3	50.8
Once a day	27.6	34.7	44.1
Less frequently	1.6	3.0	5.1
Most recent dental visit, %			
Less than 1 year ago	57.9	61.4	53.4
1–2 years ago	27.5	26.3	25.0
≥ 3 years ago	14.6	12.3	21.6
Frequency of physical exercise, %			
2–3 times a month or less frequently	23.5	28.9	44.0
Once a week	18.6	25.0	19.0
2–3 times a week	37.9	37.9	29.8
Daily or 4–6 times a week	19.9	8.2	7.1
Alcohol consumption, %			
0 g / day	10.3	8.9	11.6
< 3.0 g / day	33.2	21.6	27.9
≥ 3.0–11.1 g /day	30.8	25.4	20.9
> 11.1 g / day	25.6	44.1	39.5
Number of teeth, mean (SD)	26.7 (1.9)	26.6 (1.8)	26.1 (2.4)
Number of teeth with plaque, mean (SD)	6.0 (6.5)	7.2 (6.9)	8.4 (7.7)
BOP, % of sites, mean (SD)	27.5 (18.4)	30.4 (19.7)	36.1 (18.3)
Number of sites with PD ≥ 4 mm, mean (SD)	2.6 (5.8)	3.6 (7.4)	4.6 (7.4)
Number of sites with BL ≥ 5 mm, mean (SD)	1.2 (1.8)	1.3 (2.2)	1.5 (2.3)

BOP, bleeding on probing; PD, periodontal pocket; BL, bone level.

Table 4. Metabolic syndrome (MetS) and its components at the age of 31 and 46 by gender

	31 yrs		46 yrs	
	Males (*n* = 845)	*Females* (*n* = 946)	*Males* (*n* = 845)	*Females* (*n* = 946)
Prevalence of MetS, % (*n* = 1496 at 31 yrs, *n* = 1791 at 46 yrs)	14.1	6.7	28.9	16.5
Waist circumference, % ≥ 102 cm in males, ≥ 88 cm in females (*n* = 1438 at 31 yrs, *n* = 1786 at 46 yrs)	8.8	15.5	30.8	40.4
BMI (kg/m^2), %				
< 25	52.6	69.4	30.9	47.1
25–29.9	40.6	22.1	50.3	30.9
≥ 30	6.8	8.5	18.8	22.0
(*n* = 1484 at 31 yrs, *n* = 1790 at 46 yrs)				
Triglycerides, % ≥ 1.7 mmol/l or on drug treatment (*n* = 1484 at 31 yrs, *n* = 1747 at 46 yrs)	21.1	11.2	31.1	12.6
HDL cholesterol, % < 0.9 mmol/l in males, < 1.1 mmol/l in females or on drug treatment (*n* = 1484 at 31 yrs, *n* = 1739 at 46 yrs)	2.3	3.1	7.5	5.2
Blood pressure, % ≥ 130 mmHg / ≥ 85 mmHg or on drug treatment (*n* = 1480 at 31 yrs, *n* = 1759 at 46 yrs)	55.0	24.2	68.9	48.2
Glucose, % ≥ 100 mg/dl or on drug treatment (*n* = 1475 at 31 yrs, *n* = 1572 at 46 yrs)	51.9	29.4	48.8	22.7

BMI, body mass index (kg/m^2); HDL, high-density lipoprotein.

Table 5. Association of MetS with the numbers of sites with ≥ 4 mm deep periodontal pockets (PD ≥ 4 mm) and ≥ 5 mm alveolar bone level (BL ≥ 5 mm) in the total population and in the stratified samples of never smokers, males and females using Poisson regression models [relative risk (RR) with 95 % confidence interval (95 % CI)]

	Total		*Never smokers*	*Males*	*Females*
	Unadjusted RR (95% CI)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Adjusted RR[3] (95% CI)	Adjusted RR[3] (95% CI)
Metabolic status at age 31 years					
PD ≥ 4 mm					
No Mets (reference)	1	1	1	1	1
MetS	1.5 (1.4–1.6)	1.3 (1.2–1.4)	1.4 (1.2–1.7)	1.2 (1.1–1.4)	1.3 (1.1–1.5)
BL ≥ 5 mm					
No Mets (reference)	1	1	1	1	1
MetS	1.1 (0.9–1.3)	1.0 (0.9–1.2)	1.2 (0.9–1.5)	1.2 (1.0–1.5)	0.7 (0.5–1.0)
Metabolic status between ages 31 and 46 years					
PD ≥ 4 mm					
No Mets (reference)	1	1	1	1	1
[4]MetS < 15 years	1.5 (1.4–1.6)	1.2 (1.1–1.3)	1.3 (1.1–1.5)	1.1 (1.0–1.2)	1.3 (1.2–1.5)
[5]MetS ≥ 15 years	2.4 (2.2–2.7)	1.8 (1.6–2.1)	2.2 (1.8–2.7)	1.6 (1.4–1.9)	2.8 (2.2–3.4)
BL ≥ 5 mm					
No Mets (reference)	1	1	1	1	1
[4]MetS < 15 years	1.3 (1.1–1.4)	1.1 (1.0–1.3)	1.2 (0.9–1.5)	1.2 (1.0–1.4)	1.0 (0.8–1.3)
[5]MetS ≥ 15 years	1.7 (1.5–2.1)	1.5 (1.3–1.9)	2.5 (1.8–3.4)	1.7 (1.4–2.1)	1.2 (0.8–1.9)
Metabolic status at age 46 years					
PD ≥ 4 mm					
No Mets (reference)	1	1	1	1	1
MetS	1.8 (1.7–1.9)	1.3 (1.2–1.4)	1.7 (1.5–1.9)	1.2 (1.1–1.3)	1.7 (1.5–1.9)
BL ≥ 5 mm					
No Mets (reference)	1	1	1	1	1
MetS	1.4 (1.2–1.5)	1.2 (1.0–1.3)	1.4 (1.2–1.7)	1.1 (1.0–1.3)	1.3 (1.0–1.5)

[1]Adjusted for gender, smoking, education, dental visits, number of teeth with plaque and number of tooth sites (offset).

[2] Adjusted for gender, education, dental visits and number of teeth with plaque and number of tooth sites (offset).

[3]Adjusted for smoking, education, dental visits and number of teeth with plaque and number of tooth sites (offset).

[4]No MetS at 31 years, manifest MetS at 46 years.

[5]Manifest MetS at 31 and 46 years.