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Association between diabetes and periodontitis: A cross sectional study based on findings from Tromsø 7 study.

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Abstract

The 2017 reports published by Diabetesforbundet Norway showed an estimated 378 000 people living with diabetes (28 000 with Type 1 and 350 000 with Type 2) [1]. Mealey et al. (2006) showed that diabetes increases the risk for periodontitis, influenced by inflammatory processes. The formation of inflammatory molecules (e.g. Advanced glycation end products) leads to gingival attachment loss, periodontal pockets, bleeding; and in prolonged situation, it results in alveolar bone defects and subsequent tooth mobility/loss [2]. On the contrary, a study by Kowall et al. (2015) observed that people with pre-diabetes and well-controlled diabetes are not at risk for periodontitis [3]. Due to an insufficient number of studies for diabetes-periodontitis relationship especially in Northern Norway, this cross-sectional study aims to examine the association between diabetes and periodontitis, among those who participated for dental examination of Tromsø 7 study.

Methods

Data was extracted from Tromsø 7 study (2015-2016). Those who participated in the dental examination (as a part of Tromsø 7 study) was specifically selected for this study (N= 3943). The participants who answered the question on diabetic status from the sample selected for dental examination was 3590. Baseline characteristics included in this study were age, sex, level of education, BMI and smoking. The association between diabetes and periodontitis was checked using chi-square test. Logistic regression was performed using self-reported diabetic status as the dependent variable and periodontitis as the main independent variable. The correlation between smoking and periodontitis was tested before running the final analysis. Thus, the final regression analysis for the association between diabetes and periodontitis was adjusted for age, sex, education and BMI.

Results

The prevalence of diabetes in the study sample was 5.8%. Among the diabetes group, 58.8% were assessed as having moderate/severe periodontitis. In the unadjusted model, moderate and severe periodontitis were associated with higher odds for diabetes. Since smoking was correlated with periodontitis, the variable was excluded from the final model. There was no statistically significant association between diabetes and periodontitis when the confounding factors like age, sex, education and BMI were introduced in the final regression model.

Conclusion

This cross-sectional study reported increased prevalence of diabetes among those with moderate and severe periodontitis. The results of the regression analysis showed that there was strong interference of confounding factors in the diabetes-periodontitis relationship.

Due to the lack of studies pertaining to the population in Norway, the results from this study was compared to studies in other countries. Thus, this current study will lay the foundation for future research on the relationship between diabetes and periodontitis in Norway.

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Abbreviations

AGEs: Advanced glycation end-products

BMI: Body mass index

BOP: Bleeding on probing

CAL: Clinical attachment loss

CI: Confidence intervals

CRP: C-reactive protein

DM: Diabetes Mellitus

HbA1c: Haemoglobin A1c

IDF: International Diabetes Federation

IL-6: Interleukin-6

LDL: Low density lipoprotein

MMPs: Matrix Metalloproteinases

OR: Odds ratio

PD: Periodontal depth

PDL: Periodontal ligament

RR: Relative risk

SHIP: Study of health in Pomeria

TNF – α: Tumor Necrosis factor alpha

WHO: World Health Organization

1 Introduction

The association between diabetes and periodontitis have been investigated since the 1940s [4,5]. However, in the published studies there are inconsistent results on the relationship between the two chronic diseases. The Study of Health in Pomeria (SHIP) trend (2015) showed no association between periodontitis and prediabetes and well-controlled diabetes [3]. However, a meta-analysis on prospective cohort studies by Nascimento et al. (2018) observed that participants with diabetes had increased risk of progression of periodontitis by 86% (RR = 1.86; 95% CI = 1.3–2.8) compared to non-diabetic participants [6]. One of the reasons for the observed inconsistency could be related to the method of diagnosis (or the defined cut-off values) for blood glucose and Haemoglobin A1c (HbA1c) for diabetes and periodontitis used by different researchers. The other reasons could be related to statistical power regarding sample sizes, or interference/lack of adjustments of potential confounders. Most studies on diabetes-periodontitis relationship have examined the role of confounding factors like age, sex, BMI and smoking [6,7].

1.1 Diabetes

The American Diabetic Association (2005) defined diabetes mellitus as ‘a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both’ [8]. In 1999, World Health Organization (WHO) classified diabetes mellitus into three types – Type I, Type II (accounts for 90- 95% of all diabetic cases) and gestational diabetes [9]. Type I DM occurs due to deficiency in insulin (insulin-producing cells are damaged or destroyed and stop producing insulin). Type II DM is due to the insufficient secretion of insulin (the cells have reduced/diminished ability to respond to action of transporting glucose from blood into muscles and other tissues) in the body [8]. Gestational diabetes is defined as ‘glucose intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy’, which might lead to that women are at risk to develop Type II diabetes later in their life [10]. In the 2019 classification of diabetes mellitus, WHO introduced several other types of diabetes - hybrid forms, specific cause-related diabetes due to monogenic defects of β-cell, endocrine disorders, infections (viral) [9].

1.1.1 Epidemiology of diabetes

The prevalence of diabetes among people from ages 20-79 years differs between continents [11]. The highest prevalence of diabetes among those older than 60 years were in the high-income countries. In 2019, the diabetes prevalence was almost half a billion (463 million) of the world’s population. Globally, the increase is estimated to be 51% by 2045. In Europe, the predicted increase is 15% and currently, it is the region with the maximum number of children and adolescents with Type 1 diabetes. In African region, 3 out of 5 people are undiagnosed and deaths due to diabetes under the age of 60 years (3 in 4) were also high [11].

1.2 Periodontitis

Periodontitis is the inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with increased probing depth formation, recession or both [12]. This disease is multifactorial, and the risk factors may be modifiable or non-modifiable in nature. Tobacco smoking, oral microbiota level, hyperlipidemia, obesity is classified as modifiable factors [13]. Age, genetics, pregnancy, osteoporosis and rheumatoid arthritis are non-modifiable risk factors [14]. Kassebaum et al. (2014) reviewed 72 studies from 37 countries around the world, from 1990 - 2010 and observed that the age standardized incidence of severe periodontitis was 701 cases per 100,000 person-years (2010); and the prevalence remain steady through advanced age [15].

1.2.1 Pathogenesis

In healthy gums, the periodontal tissues are capable of coping with bacterial attack through a series of host immunity mechanisms [16]. When oral hygiene practice is discontinued (or poor maintained), it leads to accumulation of microbial plaque [17]. The characteristic feature of oral microbiota (bacteria) is its adhesiveness to oral surfaces and altering the receptivity of the host epithelium [18]. According to Marsh (2006), ‘dental plaque is the community of microorganisms found on tooth surfaces as a biofilm, embedded in a matrix of polymers of host and bacterial origin’ [19]. Oral microbiota also form biofilm on mucosa and surfaces like crowns, implants, metal restorations [20]. When the balance between bacterial biofilm and host immunity is lost, it initiates gingivitis (inflammation of gums). Inflammation is a protective response, characterized by cardinal signs such as redness, swelling, heat, pain and disrupted function [16]. Gingivitis is a reversible disease, which means that gingival health

can be restored with proper daily oral care with toothbrush and interdental cleaning [16,17]. In cases of chronic inflammation, the retention of dental plaque on the tooth at the gum line can lead to gingival attachment loss. Furthermore, the calcification of plaque occurs, as known as dental calculus [21]. The deposition of calculus around the gingival sulcus can lead to periodontal ligament loss and formation of periodontal 'pocket'. These pockets become a harbor for further bacterial colonization and the immune response and progressing of these bacterial colonies can lead to destruction of alveolar bone and subsequent tooth mobility [22]. According to Page & Schroeder (1976), there are four phases of periodontal disease progression: Initial, Early, Established and Advanced. It is difficult to draw a clear distinction between the stages, as the rate of progression of periodontal infection is heavily influenced by microbial activity, types of bacteria and host immune response [17]. Figure 1 roughly illustrates the changes occurring throughout the different stages of periodontal disease.

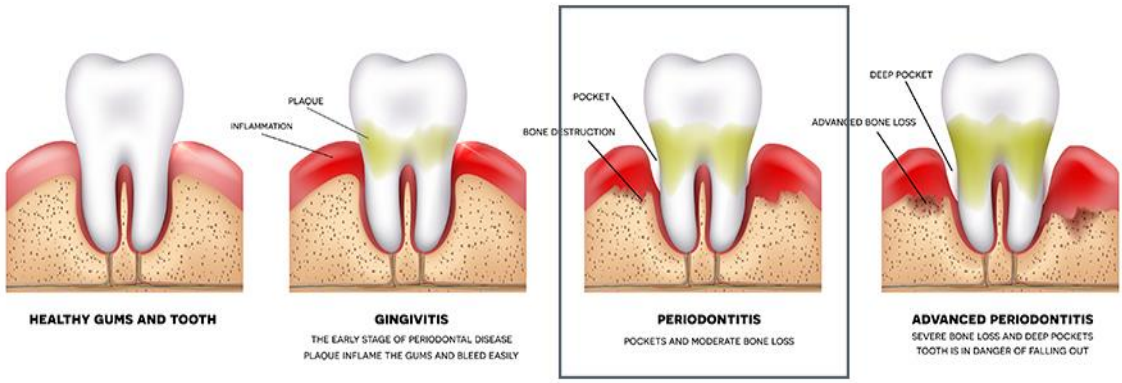


Figure 1: *Shutterstock image of periodontitis* (Illustrated by Tefi) [45]

1.3 Risk factors

Uncontrolled or poorly controlled diabetes is found to increase the risk of dental infections, due to the elevation in inflammatory molecules leading to tissue destruction and vascular injury, along with significant oral changes (i.e. reduction in alveolar bone, inflamed and bleeding gums, periodontal pockets, etc.) [23]. A pathway of periodontal infection among those with uncontrolled diabetes is shown in figure 2.

There are some common risk factors which influence the relationship between diabetes and periodontitis. For example, smoking is an established risk factor for periodontitis. However, chronic smokers were seen to have less gingival bleeding on probing compared to non-smokers [24, 25]. A study by Holde et al. (2020) studied the effect of smoking on bleeding on probing (BOP) for plaque sites in gingival marginal areas. The results from the study are as follows: the overall odds for BOP for current smokers were less than those for non-smokers (OR in current smokers= 1.45; OR in non-smokers≈ 2.2). It was also seen that odds for BOP were less in participants aged 45-68 years than those in 20-34-year category. This showed that BOP in gingival margins in current smokers were less, considering the role of smoking-related factors such as duration and exposure of smoking [26].

The incidence of diabetes was also seen to be associated with smoking. A meta-analysis by Willi et al. (2007) found that active smokers had an increased risk of Type 2 diabetes incidence compared to non-smokers (Pooled RR: 1.42; 95% CI= 1.34 – 1.51). There was increased risk of visceral obesity among smokers, influenced by high cortisol levels (the stimulation of sympathetic nervous system caused by smoking, releases cortisol). Chronic smoking also increases inflammatory markers, oxidative stress and impairs endothelial function; thus, leading to insulin resistance [27].

In older individuals, the process of aging may decrease insulin sensitivity and lead to alteration of β-cell function. The main factor influencing insulin resistance in older adults is the loss of muscle mass and accumulation of central obesity (fat deposition in the abdominal areas of the body) [28]. A cross-sectional study by Holde et al. (2017) observed that radiographic bone loss of more than 10% and PD ≥ 6mm were seen predominantly in oldest age category (65-79 years) compared to youngest category (20-34 years). In the same two groups, there were difference in the prevalence of DM (% of DM participants in 20-34 years category and 65-79 years category were 0.7% and 11.8%, respectively). The other factors considered for the study were toothbrushing habits, frequency of dental visits, smoking and socio-demographic variables. In the oldest age category, the participants had good toothbrushing habits, yearly dental visits and less smokers (never smokers were highest in the oldest age group). This showed that the presence of diabetes mellitus was an influencing factor for periodontitis, apart from age [29].

Chronological ageing can lead to ageing of periodontium; and combined with poor oral hygiene practices can potentially increase the risk for periodontitis [30]. Ageing leads to reduced proliferative activity of periodontal ligament (PDL) cells. There is increased response to bacterial activity, resulting in gingival and periodontal inflammation. Thus, ageing may be considered a risk factor (not a causal factor) for poor periodontal health, and strongly influenced by systemic diseases, oral health factors (oral hygiene practices and frequency of dental visits) [30].

Abdullah et al. (2010) conducted a meta-analysis of prospective cohort studies, evaluating the relationship between obesity and type 2 diabetes. It was seen that the pooled relative risk of

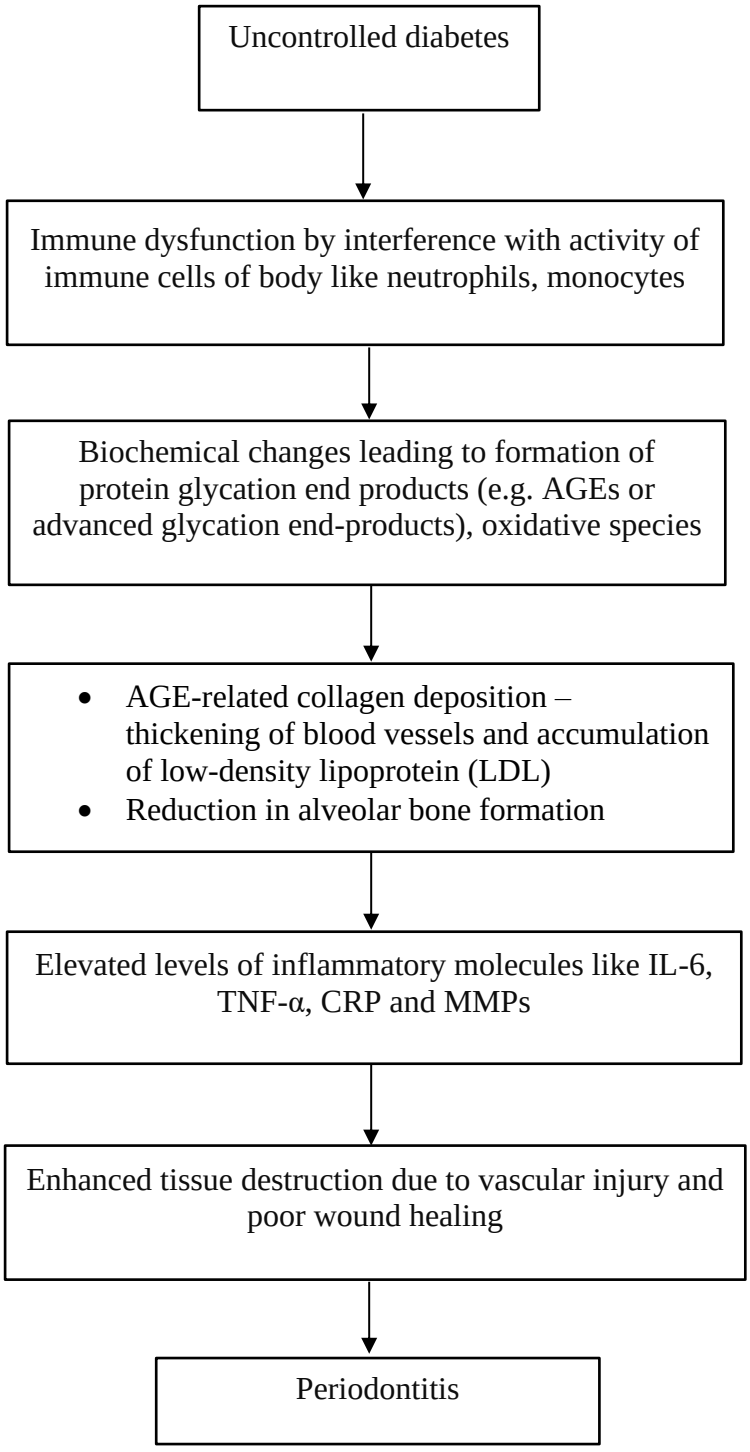
type 2 diabetes among obese participants, as compared to those with normal weight was 7.19 (95% CI= 5.74 – 9.001; p-value < 0. 001) [31].

A systematic review by Martinez-Herrera et al. (2017) evaluated 28 studies for effect of obesity on periodontitis (11 studies had defined diabetes as confounding factor). The review summarized that as insulin resistance develops due to chronic inflammation and oxidative stress, thus obese individuals may have worse periodontal health than healthy individuals. It is to be noted that obesity does not lead to periodontitis but combined with insulin resistance, can worse oral health [32].

There is a lack of research on association between diabetes and periodontitis among Norwegian population. Since Norway does not have a diabetes register, this study aims to examine the association between diabetes mellitus (type 1 and type 2) and periodontitis as a part of the Tromsø 7 study (2015-2016) using a cross-sectional design. The results from the study will add to the existing knowledge of this relationship between the two chronic diseases.

Figure 2 – A simplified flowchart on the pathological mechanism of periodontitis in diabetic individuals - based the article on 'Diabetes and periodontal diseases' by Mealey & Oates (2006)

Acronyms: IL-6 = Interleukin-6, TNF – α = Tumor Necrosis factor alpha, CRP = C-reactive protein, MMPs = Matrix Metalloproteinases [23]



2 Methodology

2.1 Study settings

Tromsø is a municipality belonging to Troms and Finnmark county of Norway, with a population of 76, 974 (2020) [33]. The Tromsø study was initiated in 1974 to investigate the risk factors of cardiovascular diseases, which was highly prevalent in the most northern parts of Norway during that time. In the later years, the study has expanded to include other diseases, lifestyle factors and behavioral factors (Tromsø 1 – Tromsø 7) [34].

2.2 Study materials

For the Tromsø 7 study, with data collection in 2015-2016, invitations to participate contained questionnaires and a brochure, along with digital login options, were sent via mail to 32,591 adults aged 40 years and above, residing in Tromsø municipality. There were 21,083 individuals who agreed to participate in the study, which corresponded to a response rate of 64.7%.

In the questionnaire Q1, the question on diabetic status (do you/did you have diabetes) was answered by 20,479 participants. In a subsample of the main study, 3943 participants were invited for a dental examination (18.7% out of 21,083 participants). There were 3695 participants who had valid results for periodontal examination (94%). Trained examiners performed the dental examination on 3695 participants and the overall periodontal status of these participants was determined. [35].

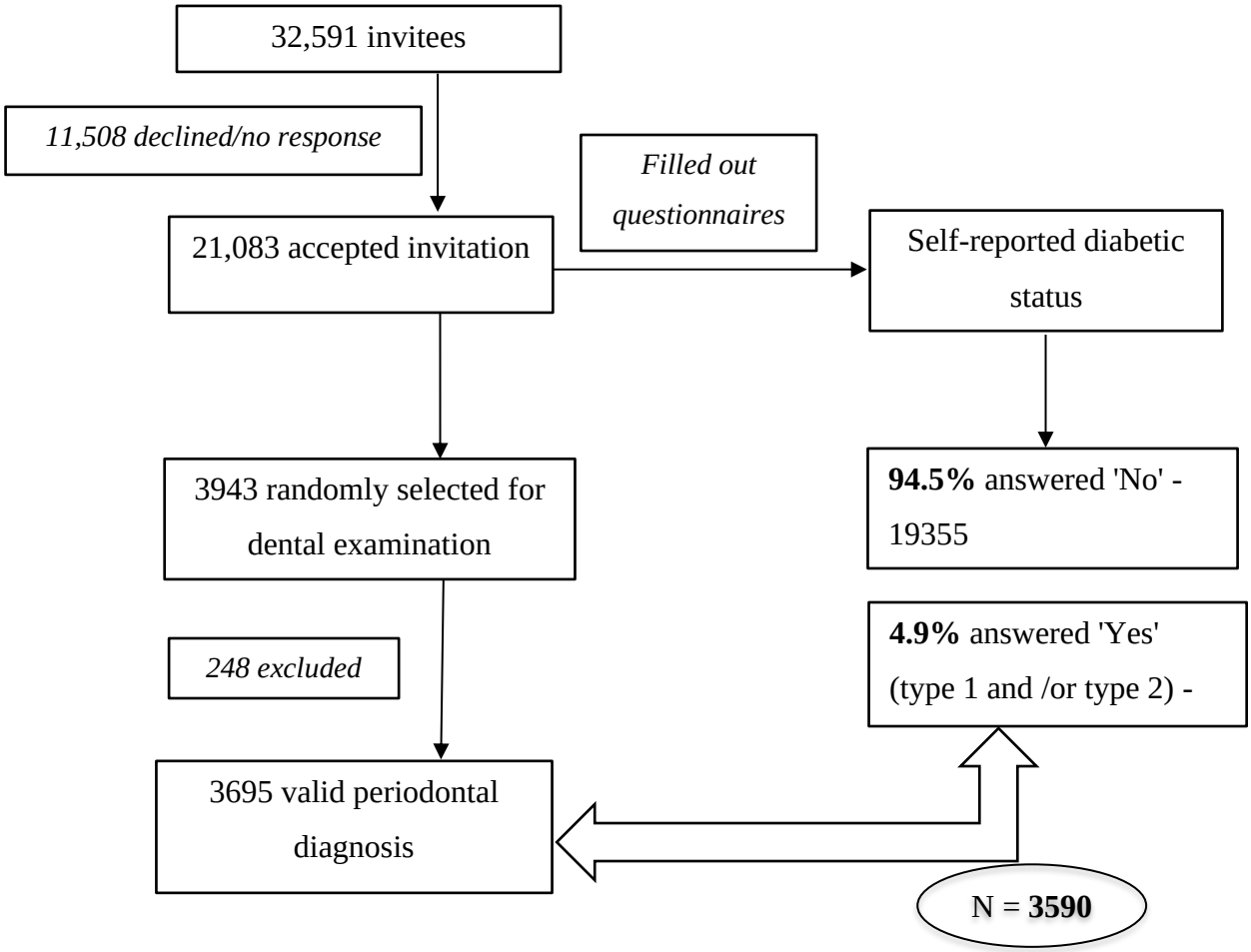


Figure 3: Flowchart depicting the selection of participants from Tromsø 7 study [35]

2.3 Description of data collected

Diabetes: based on the self-reported questionnaire, it is defined as No/Yes/Yes previously.

Periodontitis: categorized by the dental examiner as healthy, mild, moderate and severe periodontitis. The criteria used to differentiate the stages of periodontitis based on severity was taken from the article by Holde et al. (2017) (shown in Table 1).

Age: defined as the age of the participant at the time of enrollment for the study.

Sex: Male/Female

Educational level: based on years of education –

- Primary= Up to 10 years of schooling
- Secondary= primary education + 3 years of upper secondary education
- Tertiary 1= University education (less than 4 years)
- Tertiary 2= University education of at least years

Body mass index (BMI): the height and weight of the participant was measured during enrolment for the study, and BMI were calculated using the kg/m^2 formula.

Smoking: the participants were asked in the questionnaire 'Do you/Did you smoke daily' and could answer 'No', 'Yes, now' or Yes, previously'.

Table 1: Criteria for severity staging of periodontitis as defined during the Joint EU/USA Periodontal Epidemiology Working Group has suggested Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) case definitions [29].

Severity	**Clinical attachment loss (in mm) and Probing depth (in mm)**
Severe	≥ 2 interproximal sites with ≥ 6 mm CAL (not on the same tooth) and ≥ 1 interproximal site with ≥ 5 mm PD
Moderate	≥ 2 interproximal sites with ≥ 4 mm CAL (not on the same tooth) And ≥ 2interproximal sites with ≥ 5 mm PD
Slight/Mild	≥ 2 interproximal sites with ≥ 3 mm CAL (not on the same tooth) And ≥ 2interproximal sites with ≥ 4 mm PD or ≥ 1 interproximal site with ≥ 5 mm periodontal probing depth

CAL: Clinical Attachment loss PD: Probing depth

2.4 Preparation for statistical analysis

The dependent variable 'Diabetes' was collapsed into two categories (Yes, No). Since diabetes is a non-curable disease and there were few participants in the (yes, previously) category (N=116), the participants who responded 'yes, previously' were added to the group who had diabetes. The main independent variable 'Periodontitis' was divided into four categories as:

- No periodontitis
- Mild
- Moderate
- Severe

Co-variates:

1. Age: the variable was grouped into 10-year age categories = 40-49, 50-59, 60-69, 70+ groups.
2. Sex: categorized as Females/Male.
3. Educational level: depending on the years of schooling/university education, there were four main categories –
    - Primary
    - Secondary
    - Tertiary 1
    - Tertiary 2
4. BMI: the initial four categories (underweight, normal, overweight and obese) was regrouped into three categories which was entered as–

- Normal (underweight + normal)
- Overweight
- Obese

5. Smoking: the variable was included as Never, Current and Former.

2.5 Statistical analysis

The analyses were done using IBM SPSS software version 26.0. Selected characteristics of the participants with percentages, mean and standard deviations were reported. A chi-square test was performed to check the association between diabetes and periodontitis.

A binary logistic regression was performed to estimate odds ratios (OR) and the 95% confidence intervals (CI) with p-values in the association between diabetes and periodontitis. The outcome/dependent variable was diabetes and main independent/exposure variable was periodontitis; the regression model was adjusted for confounders such as age, sex, educational level, BMI and smoking. A univariable regression (unadjusted) was done between diabetes and periodontitis. Since smoking is an established risk factor for periodontitis, Pearson correlation test was performed between smoking and periodontitis. Finally, multivariable regression was performed adjusting for all the co-variates. The missing values for the variables for Age and Sex (N= 0), Educational level (N= 49), BMI (N= 8) and Smoking (N= 36), were excluded from the analysis.

2.6 Ethical considerations

The permission to receive the necessary data was obtained from UiT Arctic University of Norway and the data delivery committee at the Tromsø study. Since the data is anonymous, an ethical approval was not required to conduct this study. The data was protected in a password protected computer and was deleted after the completion of this study.

3 Results

3.1 Characteristics of demographic factors

The number of participants included in this study was 3590 who answered self-reported diabetic status from the selected group for dental examination (No diabetes= 3381, Diabetic= 209). The mean age for non-diabetics and diabetics were 53 years and 57 years respectively. Males comprised 51.3% of the total sample. It was seen that more than half of the study sample had primary and upper secondary education (51.2%) as compared to 47.4% with college/university education (Table 2). The participants in the 60 - 69 year category constituted for a major fraction of diabetes than the other age groups. A higher proportion of women reported diabetes (56.9%) as compared to the male participants (43.1%). Participants who had primary and secondary education had twice the frequency (65.5%) of diabetes than those who reported having university education (33%).

3.2 Behavioral factors

Table 2 shows that the major proportion of participants who reported having diabetes were overweight/obese (Overweight and diabetic= 35.4%; Obese and diabetic= 46.4%). Among the non-diabetic group, it was observed that 44% were former smokers and 41.5% were non-smokers. There was high proportion of former smokers in the diabetic group (50%).

Table 2: Characteristics of the study population included in the Tromsø 7 study in relation to **diabetes** outcomes.

	Diabetes= No	Diabetes= Yes	
Variables	**Frequency** (%)	**Frequency** (%)	**Total** (%)
Total number of participants (N)	3381 (94.2)	209 (5.8)	**3590** (100)
Periodontal diagnosis			
• Healthy	921 (27.2)	43 (20.6)	964 (26.8)
• Mild	805 (24)	43 (20.6)	848 (23.6)
• Moderate	1292 (38.2)	95 (45.4)	1387 (38.6)
• Severe	363 (10.7)	28 (13.4)	391 (10.9)
Age (10-year groups)			
• 40 – 49	1004 (29.7)	33 (15.8)	1037 (28.9)
• 50 – 59	988 (29.2)	49 (23.4)	1037 (28.9)
• 60 – 69	876 (25.9)	69 (33.0)	945 (26.3)
• 70 +	513 (15.2)	58 (27.8)	571 (15.9)
Mean ± Standard deviation	52.93 ± 11.022	57.94 ± 11.439	
Sex			
• Male	1751 (51.8)	90 (43.1)	1841 (51.3)
• Female	1630 (48.2)	119 (56.9)	1749 (48.7)
Educational level			
• Primary	750 (22.2)	74 (35.4)	824 (22.9)
• Secondary	981 (29.0)	63 (30.1)	1044 (29.1)
• Tertiary 1	680 (20.1)	34 (16.3)	714 (19.9)
• Tertiary 2	924 (27.3)	35 (16.7)	959 (26.7)
BMI			
• Normal weight	1097 (32.4)	37 (17.7)	1134 (31.6)
• Overweight	1499 (44.3)	74 (35.4)	1573 (43.9)
• Obese	778 (23.0)	97 (46.4)	875 (24.4)
Smoking			
• Never	1402 (41.5)	70 (33.5)	1472 (41)
• Current	454 (13.4)	32 (15.3)	486 (13.5)
• Former	1506 (43.9)	104 (49.8)	1610 (44.8)

3.3 Percentage of participants with periodontitis

From Table 2, it was observed that in the non-diabetic group, 38.2% had moderate periodontitis and approximately 11% with severe periodontitis. It was seen that 27.2% of non-diabetic participants had healthy oral status. The diabetes group had approximately 59% of participants with moderate and severe periodontitis. The number of diabetic participants in both the healthy and mild periodontitis categories was found to be equal (Table 2).

3.4 Association between diabetes and periodontitis

The Chi-square test of association between diabetes and periodontal diagnosis showed a statistical significance of 0.044 and suggests that diabetes is associated with periodontitis in this study sample. The unadjusted logistic analysis of the association between diabetes and periodontitis showed that the odds for diabetes among the participants with moderate periodontitis was 57.5% higher than those with healthy oral status (OR= 1.57 [95% CI= 1.09 – 2. 28]). There was 65.2% higher odds for diabetes among the participants with severe periodontitis than (OR= 1.65 [95% CI= 1.01 – 2.70]).

Since smoking was strongly correlated with periodontitis (Correlation coefficient= 0.14), the variable was excluded from the final model. With the adjustment for covariates (age, sex, educational level and BMI) in the final model, all the effect estimates decreased (Mild; OR= 1.03, [95% CI=0.67 - 1.60], Moderate; OR=1.12 [95% CI= 0.76 - 1.65], Severe; OR=0.99, [95% CI=0.59 - 1.67] and were no longer statistically significant for diabetes.

Table 3: Odds ratios (OR), 95% confidence intervals (CI) for the association between diabetes and periodontitis in the adult population of Tromsø 7 study.

	Univariable model		**Multivariable model**	
Periodontitis diagnosis	OR (95% CI)	p-value	OR (95% CI)	p-value
Healthy	Reference		Reference	
Mild	1.14 (0.74 – 1.76)	0.542	1.03 (0.67 - 1.60)	0.892
Moderate	1.57 (1.09 – 2.28)	0.016	1.12 (0.76 - 1.65)	0.559
Severe	1.65 (1.01 – 2.70)	0.045	0.99 (0.59 - 1.67)	0.976

Adjustment variables in the multivariable model**:** Age, sex, educational level, BMI. The values for odds ratios and confidence intervals are rounded to the nearest decimal.

4 Discussion

4.1 Summary of findings

This cross-sectional study investigated the association between diabetes and periodontitis, among adults who participated in the dental examination of the Tromsø 7 study.

The results showed that a major proportion of participants (58.8%) who were diabetic had moderate and severe periodontitis. Even though findings from the crude model showed significant association between periodontitis (moderate and severe categories) and diabetes; no statistically significant association was seen between diabetes and periodontitis in the adjusted model. These results suggest that there was a strong interference of the confounding factors like age, sex, educational level and BMI in the study sample.

4.2 Prevalence of diabetes in Norway

The current study revealed that there was no relationship between diabetes and periodontitis in the sample of 3590 individuals. There is no diabetes register for Norway yet, hence the comparison between the true prevalence of diabetes and the prevalence in this study sample is

challenging. Based on the results from studies published on diabetes from 2014 – 2018, the International Diabetes Federation (IDF) estimated the prevalence of diabetes in adults in Norway at 7.5% and the percent of undiagnosed diabetes was 36.3% (20 – 79 years) [36]. On the other hand, the data published by Norwegian Institute of Public Health (NIPH) in 2017, the prevalence of diabetes is estimated to 4.7% [37]. The inconsistency seen in the prevalence estimates further highlight the need for high quality studies finding the true prevalence of diabetes to be conducted in the population in Norway.

4.3 Findings compared to other similar studies

In the present study, the prevalence of diabetes was 5.8%. A cross-sectional study by Holde et al. (2017) reported 3.8% of diabetes prevalence among those with periodontitis in a sample of 1911 adults in Norway [29]. Aimetti et al. (2015) reported results on diabetes prevalence among those with moderate and severe periodontitis (5.3%), as seen in 736 participants in Italy [38]. There has been reports published on the prevalence of oral diseases/conditions or use of dental services by NIPH but the information regarding the actual prevalence of periodontitis is limited.

The results of logistic regression analysis showed no association between the diabetes and periodontitis in this study. Similar results were obtained by Aimetti et al. (2015) in which the adjusted logistic regression model did not show any statistically significant association between diabetes and periodontitis (OR: 2, 95% CI= 0.64-6.24); adjusted for age, gender, education and smoking.

It was reported by International Diabetes Federation (2019) that the highest prevalence of diabetes were seen among African and South-East Asian population. Even though the reported prevalence of diabetes was low in Europe, the methods used to assess the overall prevalence were not reliable (i.e. based on observational studies which had self-reported diabetes) [11]. For instance, a systematic review by Ziukaite et al. (2017) investigated the prevalence of diabetes among those with periodontitis based on 27 studies (cross-sectional, case-control and cohort designs) [39]. The search strategy specified that the authors included papers that had diabetes as the outcome variable. Findings showed that overall diabetes prevalence among the subjects (N=29,594) with periodontitis was 13.1% and those without periodontitis was 9.6%. It has been observed that the highest prevalence of diabetes among those with periodontitis is found in Asian population (17.2%), and the lowest prevalence was among European population (4.3%). The reason for low prevalence of diabetes among European populations was suggested by the authors that the included studies conducted in Europe had only self-reported diabetes, which underestimates the risk of diabetes in those population [39].

Since cross-sectional studies cannot be used to explain causal pathways, the possibility of a bidirectional relationship between diabetes and periodontitis cannot be excluded. For example, Nascimento et al. (2018) conducted a meta-analysis which diabetes increased the risk of incidence or progression of periodontitis by 86% (RR= 1.86; 95% CI 1.3–2.8). The major drawbacks of the review was high heterogeneity between the results and inclusion of cross-sectional studies [6]. Even though the question of whether periodontitis and diabetes have an association persists, there have been studies which observed that periodontitis was associated with the complications of diabetes. According to Sanz et al. (2018), based on analyses of 14 studies (N= 31,988), periodontitis was associated with diabetic complications

such as retinopathy, nephropathy, neuropathic foot ulceration, cardiovascular disease, death due to cardiorenal disease (see the definitions of the terms in the appendix section) [40]. Moreover, the association between periodontitis and diabetes-related complications was also evaluated through a systematic review by Borgnakke et al. (2013). The review was based on seven studies (four cohort and three cross-sectional designs) which assessed either Type 1, Type 2, or unspecified. Periodontitis was assessed clinically using the measures – clinical attachment loss (CAL), periodontal probing depth (PPD), bleeding on probing (BOP), and number of teeth present; radiographic assessment was also done in some studies. It was seen that type 1 and type 2 diabetes along with poor periodontal health (especially severe periodontitis) had higher risk for diabetes-related complications than those with mild periodontitis and healthy oral status [41].

The limitations were that most of the included studies in the systematic reviews and meta-analyses had cross-sectional design, differing in sample size, used different diagnostic criteria for diabetes and periodontitis or had high-risk population as their study group. Despite these limitations, the results from different countries showed that the prevalence and odds of diabetes differs across the populations. This current study is one of the few studies in Norway which examined the association between diabetes and periodontitis in Norway. It was observed that the adjusted regression analysis showed no association between diabetes and periodontitis using data from the Tromsø 7 study. This finding was analogous to Kowall et al. (2015), who also reported no association between periodontitis and well-controlled diabetes [3]. It is unclear whether the participants in the current study had well-controlled or poorly controlled diabetes. Due to limited information on the time of diagnosis for both diabetes and periodontitis in the sample and being a cross-sectional study, it was not possible to derive conclusion on which chronic disease preceded the other. However, the findings emphasizes

the need for high quality longitudinal studies discussing the association between the two chronic diseases among the Norwegian population.

4.4 Methodological considerations

The Tromsø 7 study included 21,083 participants, out of which 3943 participants were invited for the dental examination (18.7%). Among this group, there were 248 participants who were excluded (few teeth, absence of X-rays etc.), which resulted in a total of 3695 participants with valid cases of periodontal diagnosis. The participants were divided into four groups, depending on their overall periodontal diagnosis. The data was sorted so that participants who answered the question on their diabetic status and underwent periodontal examination were selected (N= 3590). Since this is a cross-sectional study, the data for each individual was collected during the same period (2015-2016) and with no follow-up, it is not possible to establish causal relationship (either diabetes leads to periodontitis or vice versa). The results from this study shows that the role of confounding factors in the diabetes-periodontitis relationship is important, thus further research in this topic is crucial.

4.4.1 Selection bias

Selection bias occurs when eligible participants, or follow-up time of some participants, or outcome events, are excluded in a way that leads to the association between exposure and outcome different from actual association [42]. This type of bias also occurs due to missing data on the participants on selected baseline characteristics. In this study, there were 3943 participants randomly selected for dental examination out of 21,083 participants. This process of random selection reduces the risk of selection bias, as it is based on chance (every participant is likely to be either selected/not selected) [43].

4.4.2 Information bias

This type of bias arises when there is misclassification or any error in measurement of the exposure, outcome and other factors [42]. For the Tromsø 7 study, diabetic and smoking status was assessed through self-reporting in questionnaires. During enrollment, the diabetic status was validated through blood test for serum glucose. However, the blood glucose levels were not considered for this study. The reliability of self-reported diabetes for this study is questionable. The response bias occurs when the participants do not report accurately, and in this context, due to social desirability factors (falsely reporting the smoking habits or other behaviors) [44]. This could be a reason for low prevalence of current smokers in this study sample. Despite few current smokers, there was a strong correlation between periodontitis and smoking. The height and weight of participants were measured by examiners during the enrollment of Tromsø 7 study. Even though there are possibilities for discrepancies in the measurement or calculation of BMI, it is uncertain if it can affect the results of this study.

4.5 Strengths and limitations

This cross-sectional study is one of the few observational studies identifying the association between diabetes and periodontitis, especially based on participants from Northern Norway. The limitations of this study were that it was not possible to derive causal relationship between diabetes and periodontitis. There was relatively small sample size, as compared to the total number of participants for the Tromsø 7 study (3590 vs 21,083). Among this group, there were a small percent of missing information. Moreover, this study is not representative of the entire population of Northern Norway, as the study sample was small. Despite these limitations, the results, however, can lay foundation for high quality research in the future.

5 Conclusion

This cross-sectional study was one of the few studies which reported the odds of diabetes among participants with periodontitis from Tromsø 7 study. In the crude model, participants with moderate and severe periodontitis had increased odds for diabetes. However, the adjusted regression model showed that the confounding factors such as age, sex, education, BMI and smoking influenced the diabetes-periodontitis relationship, suggesting no association. Due to the various limitations in this cross-sectional study like small sample size, using data which were not validated, and lack of updated studies, future research on the relationship between diabetes and periodontitis in Norway is necessary.

6 References

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7 Appendix

1. Retinopathy (diabetic): Damage to blood vessels in the retina (swelling, leaking of blood, abnormal growth of blood vessels in retina) caused by high blood sugar levels, leading to vision impairment [46]
2. Nephropathy (diabetic): Diabetic nephropathy is defined by a raised urinary albumin excretion of >300mg/day (indicating clinical proteinuria) in a patient with or without a raised serum creatinine [47].
3. Neuropathic foot ulceration/ 'Diabetic foot': Polymicrobial infection of bones and soft tissues in the lower extremities (foot and digits) in diabetic patients, especially those with vascular insufficiency [48].
4. Cardiorenal disease: defined as a bidirectional pathological impairment of either the heart or the kidney due to acute or chronic primary dysfunction in either organ [49].