Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 152-168
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

What Is Dentists' Role in Modulating Environmental and Epigenetic Determinant in Oral Health of Diabetic Patients?

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How to cite this paper: Guo, Z.Z. (2023) What Is Dentists' Role in Modulating Environmental and Epigenetic Determinant in Oral Health of Diabetic Patients? *Journal of Biosciences and Medicines*, **11**, 152-168.
https://doi.org/10.4236/jbm.2023.112011

Received: December 24, 2022
Accepted: February 14, 2023
Published: February 17, 2023

Abstract

Background and Purpose: With the unexpectedly rapid increase in the prevalence of types of diabetes worldwide, this chronic disease is no longer being viewed as a systemic health issue, but also treated as the start of the deadly disease. As the sixth complication of diabetes, periodontitis is a chronic inflammatory condition that leads directly and indirectly to a severer condition of diabetes via its underlying mechanisms. Interestingly, both diseases are not been fully identified in their bidirectional relationships by researchers. Thus, healthcare agencies must pay appropriate attention. This literature review paper aims to investigate and discuss dentists' role in modulating environmental and epigenetic determinants in the oral health of diabetic patients based on the bidirectional relationship between these diseases, their prevalence and how treatment of one disease affects the other. **Methods:** The authors conducted electronic searches in PubMed, Google Scholar, One Search UofT, ScienceDirect, and the National Library of Medicine. The paper also included gray literature from government resources related to the topic. The paper will review the epidemiology, pathogenesis, and epigenetics of both diabetes and periodontal disease and their functions with each other. **Results:** The literature has consistently shown that diabetes and periodontal disease have responded to the formation and severity of each other. Patients with pre- and diabetes have potentially higher risks of causing periodontal disease and other complications if adequate diagnosis and treatment are not involved timely. The combination of risk factors, including individual, social, environmental, and genetic, play a crucial role in the development of diabetes and the severity of periodontitis. **Conclusions:** Based on the results, the collaboration between dentists and other healthcare practitioners is inevitable in the overall development of treatment for both diseases. With the proper and updated knowledge, dentists can benefit patients' overall physical conditions through stra-

tegic intervention in diabetes patients.

Keywords

Periodontitis, Diabetes Mellitus, Epigenetic, Pathogenesis, Epidemiology

1. Introduction

There are two types of diabetes mellitus: type 1 (an absolute type caused by genetic condition) and type 2 (lifestyle-related) diabetes. The treatment was developed and first described decades ago by Banting and Best. Approximately 537 million people worldwide are suffering from diabetes, according to the World Health Organization, which is 6% of the world's population [1]. The majority of the 422 million people with diabetes worldwide live in low- and middle-income countries, and diabetes directly causes 1.5 million fatalities each year. Both the incidence and prevalence of diabetes have steadily increased over the last few decades [1]. With the prediction, researchers doubt that 97% of the population will be diagnosed with type 2 diabetes [2].

Over the decades, periodontitis has been one of the most prominent topics in research due to its irreversible and incurable characteristics. An investigation of associations between periodontal diseases and systemic diseases (including diabetes) in human populations had been announced and launched by Offenbacher in 1996 [3]. With the development of technology and the continuous passion for discovering periodontal disease, it has been well-understood that it can significantly increase the risk of osteoporosis, diabetes mellitus, severe infections at anatomic sites, and other complications [3]. The association between diabetes mellitus and periodontitis has been studied for decades. However, the underlying mechanisms between both conditions are not well-understood currently.

This literature review paper aims to investigate and discuss dentists' role in modulating environmental and epigenetic determinants in the oral health of diabetic patients based on the bidirectional relationship between these diseases, their prevalence, and how treatment of one disease affects the other.

2. Methods

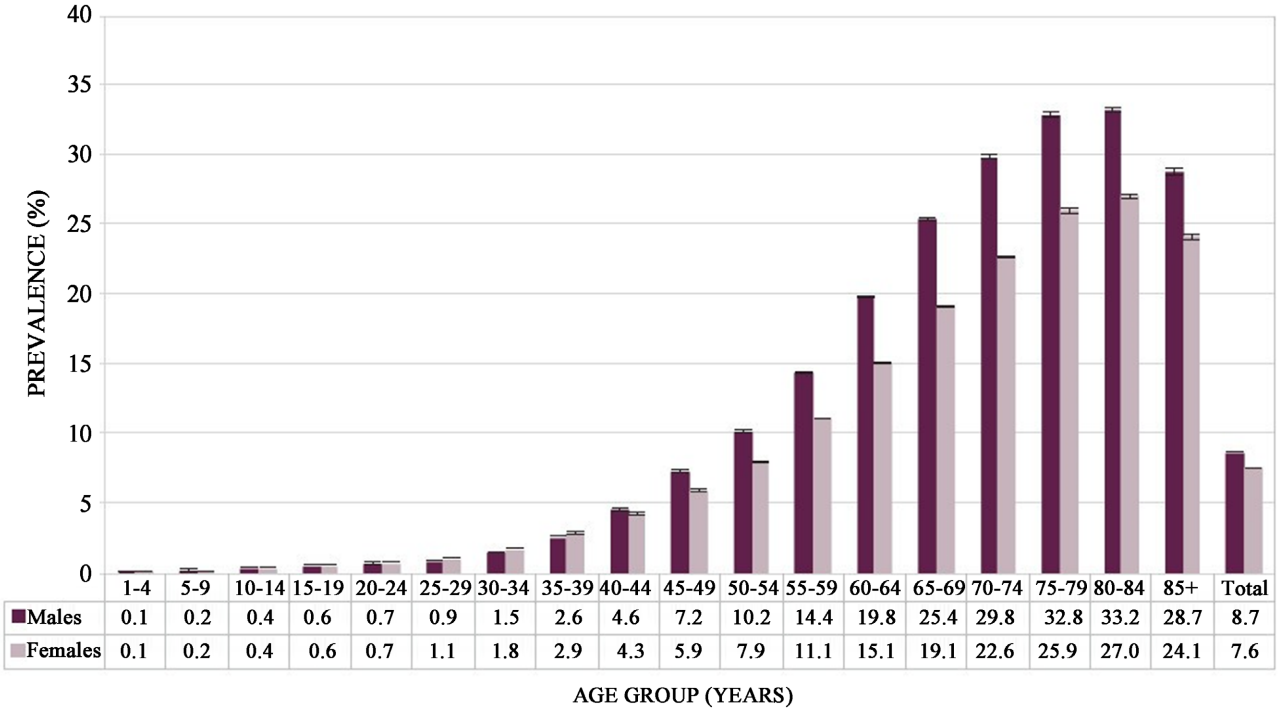
The author investigated the pathogenesis, epigenetics, and epidemiology of periodontal disease and diabetes by electronic searches on PubMed, Google Scholar, One search UofT, ScienceDirect, and National Library of Medicine, and all papers are in the English language. Additionally, the authors manually searched gray literature, including the data from Diabetes Canada, Reports from the Government of Canada, Data from the City of Toronto, Reports from Public Health Ontario, and Public Health Toronto from 2003 to February 2022. Studies with the following keywords: "periodontal disease", "periodontitis", "type 2 diabetes mellitus", "diabetes", "complications of diabetes", "epigenetic", "pathogenesis",

and "epidemiology" were selected.

3. Results

Prevalence and incidence of diabetes in Canada, Ontario, and the Great Toronto Area

As the massive population of diabetic patients worldwide, diabetes has become one of the most concerning diseases affecting Canadians. An estimated 1 in 16 people in Canada has been diagnosed with diabetes [4]. Corresponding to the data from the Public Health Agency of Canada, about 3.0 million Canadians were living with diagnosed diabetes between 2013 and 2014, representing 1 in 20 children and young adults aged between 1 to 19 years and 1 in 10 adults (20 years and older) [5]. As **Figure 1** portrays, there is a higher increase in the prevalence of diagnosed diabetes over time among males (8.7%) than the increase (7.6%) among females [5]. Within each age group, males also have a significant increase in diabetes with age than females (**Figure 1**) [5]. Nearly 200,000 Canadians were newly diagnosed with diabetes from 2013 to 2014, meaning that 5.9 Canadians recently have diabetes per 1000 population, including 0.4 new cases among children and youth and.7.6 new cases per 1000 population among adults [5]. A relative increase of 37.3% is in the age-standardized prevalence of diagnosed diabetes between 2003-2004 and 2013-2014 in Canada [5]. Following the estimated trend created by the government of Canada, A steady and continued increase in Canada, with 11.7 million Canadians living with diabetes or prediabetes in 2022. There will be 26% more people with diabetes in 2032 [6]. Based on



	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Total
Males	0.1	0.2	0.4	0.6	0.7	0.9	1.5	2.6	4.6	7.2	10.2	14.4	19.8	25.4	29.8	32.8	33.2	28.7	8.7
Females	0.1	0.2	0.4	0.6	0.7	1.1	1.8	2.9	4.3	5.9	7.9	11.1	15.1	19.1	22.6	25.9	27.0	24.1	7.6

Figure 1. Prevalence in the percentage of diagnosed diabetes by age group and sex in Canada from 2013 to 2014. Created by the Public Health Agency of Canada [5].

the Canadian Diabetes Cost Model created in 2016, an estimated 4 million Canadian live with diagnosed diabetes which is 10% of the Canadian population [7] [8]. Until February 2022, the prevalence of diabetes, including type 1 and type 2 diabetes, is 2.35 million, which is 15% among Ontarians [9]. Moreover, people with prediabetes are stealthy within the community. The total number would be climbed up to 30% of the Ontario population, 4.71 million when prediabetic patients are included [7] [8] [9]. The prevalence of diabetes in Toronto, where the University of Toronto locates, increased from 6.7% in 2003 to 10.2% in 2004 (**Figure 2**) [10]. Both the prevalence (10.2%) and incidence (6.5%) in Toronto were significantly lower than in the Greater Toronto Area (10.7% in prevalence and 6.8% in incidence excluding Toronto) but were significantly higher compared to the rest of Ontario in 2014 (9.6% in prevalence and 5.8% in incidence) [10]. The local government in Toronto had numbered the prevalence ranged from 4.6% to 16.8% among 140 major neighborhoods in the Great Toronto Area in 2014 [10]. The center areas of Toronto city, including clusters of neighborhoods around Bayview Ave, Yonge St, Bloor St W, and Southern Danforth Ave which are heightened in white had significantly lower prevalence (4.6 to 6.9%) than whole Toronto (**Figure 3**) [10]. It is easy to notice that there is a growing trend in the prevalence of diabetes (%) from the center of the city to the western and northeastern part of Toronto, highlighted from light blue to dark blue, where clusters of neighborhoods with significantly higher prevalence (more than 13.4%) than those in the center [10]. After adjustment from age-standardized Diabetes prevalence (%) to age-standardized diabetes incidence (per 1000 people), the major layout remained almost similar to **Figure 3**. However, diabetic patients' density increased in the northeastern part of Toronto [10].

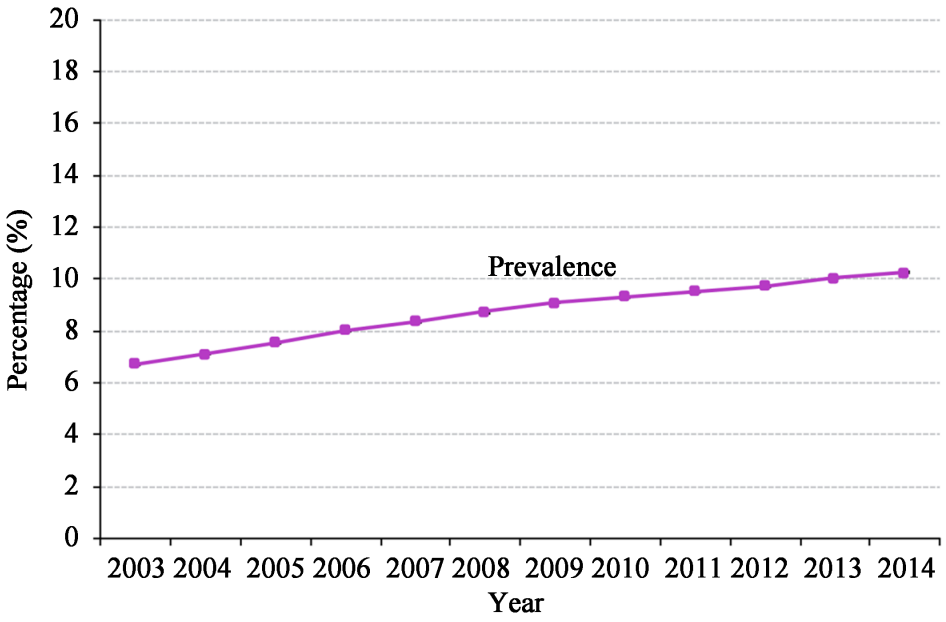


Figure 2. The change of age-standardized Prevalence of Diabetes in Toronto during 11 years from 2003 to 2014. Created by Public Health Toronto [10].

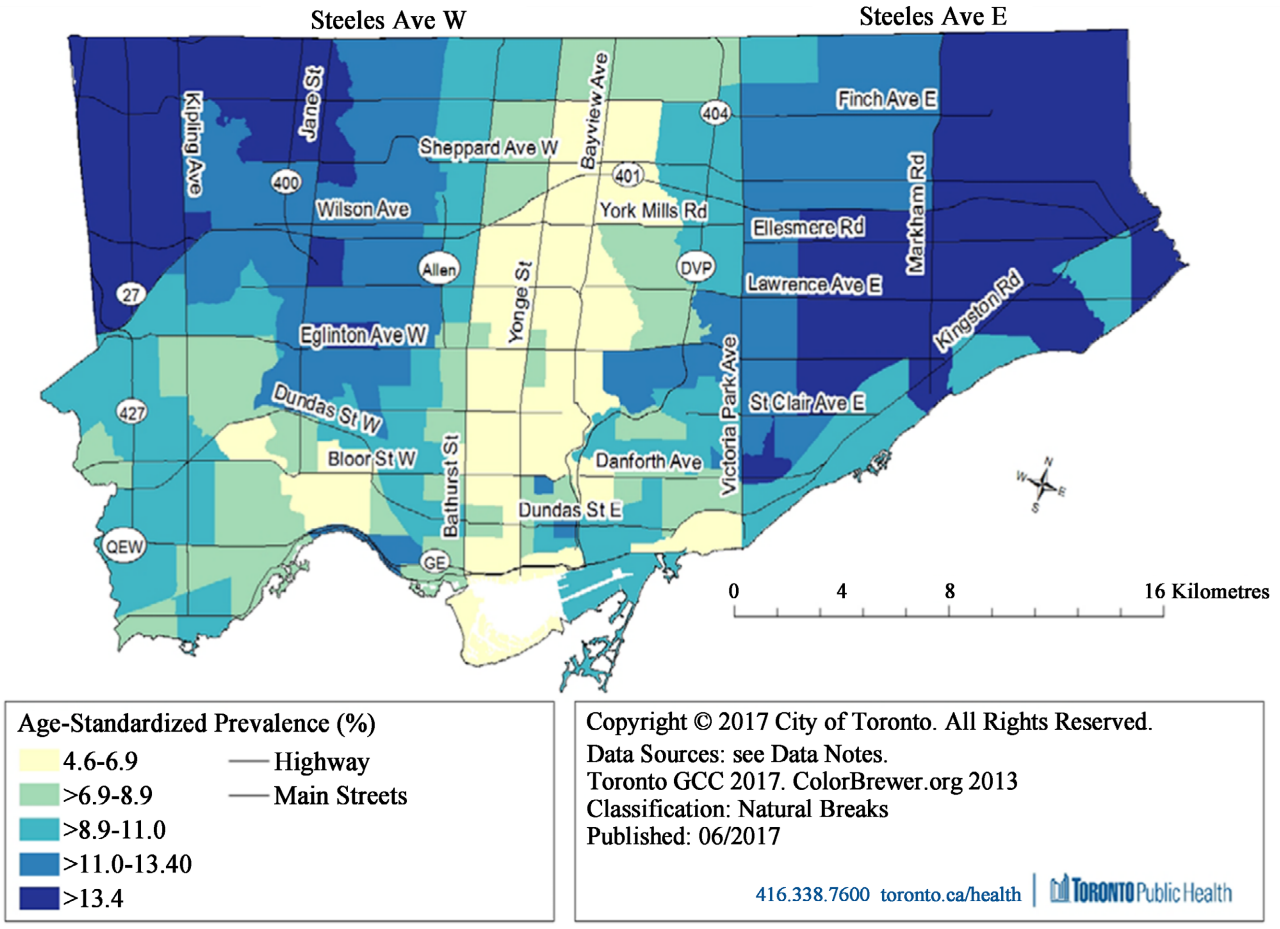


Figure 3. The layout diagram of age-standardized diabetes prevalence (%) among 140 Toronto neighbourhoods. Created by Public Health Canada (2014) [10].

Overall Harm of Diabetes and Diabetic-related Complications

Not only the high prevalence of diabetes in either Canada or worldwide is a burden to the health care system, but diabetes' tolls and its complications, which are associated with premature death and chronic diseases, are also a significant difficulty for the current society. The Public Health Agency of Canada pointed out that diabetic patients may experience a reduced 5 to 15 years lifespan compared to non-diabetic people in Canada [11]. When compared to the general population (without diabetes condition), diabetic patients are likely to be hospitalized due to different complications, including cardiovascular disease (over three times more), end-stage renal disease (12 times more), and nontraumatic lower limb amputation (nearly 20 times more) [11] [12]. The numbers are unexpected and miserable. A review paper written by Deshpande *et al.* provided general insight into the percentage of diabetes contributes to different complications, which shows that chronic kidney disease (27.8%), food problems (22.9%), and eye damage (18.9%) are the three highest appearance-conditions among patients (**Figure 4**) [13]. Diabetes Canada included more exaggerated data that diabetes contributes to 30% of strokes, 40% of heart attacks, 50% of kidney failure, and 70% of leg and foot amputations in Ontario compared to the data from

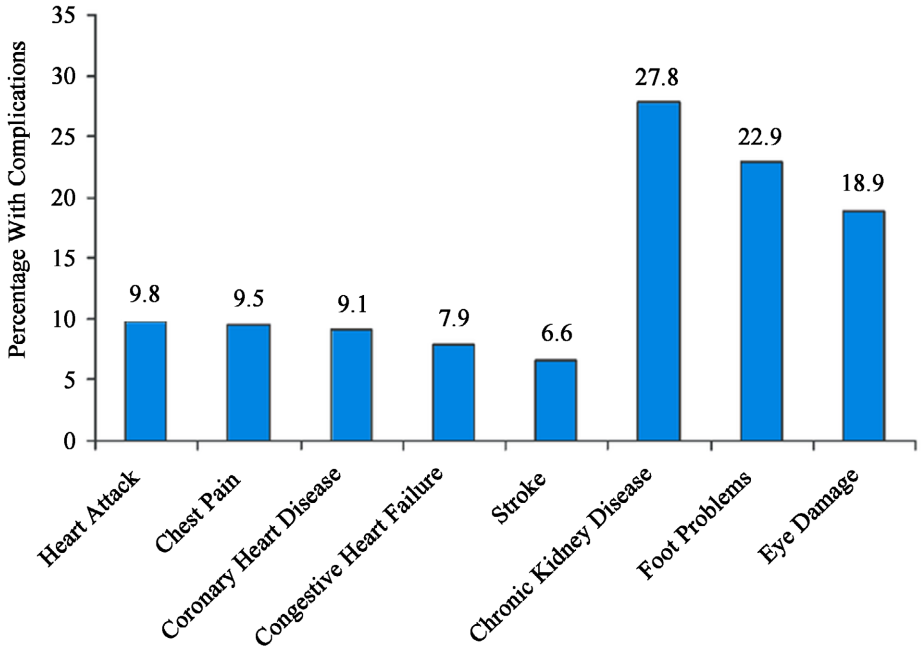


Figure 4. Prevalence of diabetes-related complications among diabetic patients. Recorded by National Health and Nutritional Examination Survey from 1999 to 2004 [13].

Deshpande *et al.* where 6.6% in stroke, 9.8% heart attack, 27.8% kidney disease, and 22.9% foot problems separately [14]. Interestingly, the prevalence of clinically relevant depressive symptoms among 30% of diabetic people and individuals suffering from depression are 40% - 60% more likely to acquire type 2 diabetes [15]. Almost one-fourth of people with diabetes are affected by foot ulceration, and one-third of amputations are operated on individuals with diabetic foot wounds [16]. Nevertheless, periodontitis is now recognized as the sixth complication of diabetes and determined as a significant issue in current society along with retinopathy, nephropathy, neuropathy, macrovascular disease, and poor wound healing based on epidemiological studies on both type 1 and 2 diabetes under poor systemic conditions [17].

Diabetes, Risk Factors, and Epigenetics

Diabetes mellitus is one of the well-known diseases that have been diagnosed and to be researched for decades. It is a metabolic condition characterized by an uncontrolled increase in blood glucose, which needs timely appropriate monitoring and control [18]. Pancreatic beta cells, known as β-cells, enable the generation of insulin, which plays a vital role in this chronic condition. Diabetes is caused by a lack of insulin synthesis or sensitivity and is divided into type 1 and type 2 diabetes.

Type 1 *diabetes mellitus*

Type 1 diabetes mellitus (T1DM) is known as insulin-dependent diabetes due to insulin deficiency meaning that no insulin or a deficient volume of insulin is secreted from the human pancreas. It is not common in adults, mainly in children and young adults, and is around 5% - 10% of diabetes prevalence in Canada [9]. Insulin is an essential hormone for the intracellular transport of glucose into

insulin-dependent and -sensitive organs and tissues, especially skeletal muscles and adipose tissue, regulating energy supply and macronutrient balance [19]. Under insulin deficiency, blood sugar cannot reach cells and accumulates inside the bloodstream, leading to damage and triggering many symptoms. The primary cause of this type of diabetes is the destruction of pancreatic β-cells through an autoimmune response, leading to a significant absence of insulin secretion [18] [19]. The exact pathogenesis of diabetes mellitus is still not well understood. In most cases, there is an interaction between genetic and environmental factors and evidence of destruction of β-islet calls by the autoimmune system [9] [18] [20] [21].

Type 2 diabetes mellitus

Compared to type 1 diabetes mellitus, type 2 diabetes mellitus (Type 2 Diabetes Mellitus) is mainly associated with abnormally increased insulin resistance. The body cannot synthesize enough insulin to overcome the elevated resistance, which poor dietary and daily behaviors may cause [18]. As a result, it is difficult for an individual to maintain homeostasis of blood sugar level under this condition, which means that insulin sensitivity will significantly fluctuate after high carbohydrate meals, intense physical activity, and stress events. Insulin gene expression will be inhibited or significantly reduced under a combination of high fatty acid and hyperglycemic environments [18]. As a result, individuals with type 2 diabetes mellitus frequently occur resistance to the action of insulin, especially in obese individuals with more adipose tissues that are crucial in producing several hormones and inflammatory mediators such as TNF-α, IL-6, and IL-1β contributing to systemic inflammation [18]. Increased inflammatory cytokines and immune cell production may result in islet inflammation in the pancreas of type 2 diabetes mellitus [18].

Risk Factors

Family history and an individual's inherent genetic factors significantly trigger in both type 1 and 2 diabetes mellitus. Environmental factors might trigger type 1 diabetes mellitus, such as viral infections leading to gene mutation, low levels of vitamin D leading to immune modulation and autoimmune system, and lower exposure to ultraviolet rays [22]. However, the exact mechanisms of type 1 diabetes mellitus are complex and still under investigation. Previous studies further illustrated that type 2 diabetes mellitus is caused by a combination of risk factors such as individual, social, environmental, and genetic factors [9] [20]. A systematic review written by Ismail *et al.* identifies the majority of potential risk factors for both incidence and prevalence of type 2 diabetes mellitus and serum uric acid, sleep quantity/quality, smoking, aging, ethnicity, and physical inactivity are highlighted [23].

Serum uric acid

Individuals with elevated serum uric acid levels will experience impaired glucose uptake in the skeletal muscles and an increase in inflammation, leading to blood glucose accumulating in the bloodstream and dysfunctional and dead β-cells [23]. From the overall results of several studies, the association between

high-level serum uric acid and type 2 diabetes mellitus is contradictory. Scientists are determining whether Serum uric acid is an independent factor for type 2 diabetes mellitus or functions between other independent risk factors and type 2 diabetes mellitus. Some studies support a positive relationship between high serum uric acid and the incidence of type 2 diabetes mellitus [24] [25] [26]. In contrast, others believe no significant association [23] [27]. Undoubtedly, the serum uric acid level should be an inseparable potential risk of type 2 diabetes mellitus regardless of the former concerns.

Sleep

Moreover, abnormal, disturbed, and reduced quality and quantity of sleep are associated with glucose intolerance, which is affected by social, psychological, environmental, and behavioral factors [23] [28]. Individuals with a sleep disorder may experience a deficiency in oxygen reaching the tissues while sleeping and inflammation, triggering an increase in sympathetic activity that leads to insulin resistance resulting in type 2 diabetes mellitus [23] [29]. Ismail *et al.* mentioned that individuals who have sleep duration of around 7 to 8 hours might have a lower risk of developing type 2 diabetes mellitus than those who have either less than 6 hours sleep or more than 8 hours sleep [23]. Furthermore, individuals who are difficulty initiating sleep (DIS) are associated with the incidence of type 2 diabetes mellitus, which means that the more frequent lousy sleep those patients have, the higher risk of developing type 2 diabetes mellitus [30]. Interestingly, there is a stronger association between women sleeping for more duration and increased risk of incident diabetes, whereas men who sleep for short sleeping duration also have a relatively higher risk than women [31].

Smoking

Smoking is a universal risk factor for diverse chronic diseases, pain, and lethal cancers, leading to over 8 million deaths annually [32]. Increased level of nicotine in both passive and active smokers leads to reduced glucose intake in human muscles, further developing insulin resistance, and eventually type 2 diabetes mellitus appears [33]. Studies included in Ismail *et al.*'s review paper showed that the risk of incidence type 2 diabetes mellitus is strongly associated with both active and passive smokers especially in men smokers [34] [35] [36]. However, the exact association between ex-smokers and the incidence of type 2 diabetes mellitus is due to serval contradictions [37] [38] [39].

Aging

With aging, the body's various functions, including metabolic functions, will gradually become slow and even exhausted. Without a doubt, aging increases chronic inflammation in the elderly which is potentially occurring in type 2 diabetes mellitus [23]. Moreover, accumulation of body fat leads to elevated free fatty acids (FFAs) concentration caused by lipid metabolism disorder in elderly individuals, which has high risk of development in type 2 diabetes mellitus [40]. Although some studies supported the association between aging and increased incidence of type 2 diabetes mellitus, insufficient research and evidence might be a limitation to support the hypothesis that aging is an independent risk factor for

type 2 diabetes mellitus.

Ethnicity

Ethnicity is strongly related to various factors, including genetics, income, living environment, intake, and lifestyle, making it an independent risk factor for Type 2 Diabetes Mellitus. From the latest report by Diabetes Canada, specific ethnic groups, including African, Arab, Asian, Hispanic, Indigenous, or South Asian descent, have been listed and mentioned in many pieces of literature to have a significantly higher risk of having diabetes in Canada. Among all Canadians, South Asian descent has the highest prevalence rate for diabetes among the former listed risk-ethnic groups which is 14.5% among this race and Arab/West Asian descent is the lowest which is 7.5% [9]. The prevalence of diabetes is 8.1 times higher in South Asian and 6.6 times higher in Black adults than in White adults [9]. Zimmet *et al.* determined that rural Indians have 10 time times higher risk of developing type 2 diabetes than rural Melanesians, and urban Melanesians have 2 times lower risk than those urban Indians [40]. Physical activity in rural areas is relatively increased compared to the urban areas in Indians and Melanesians could be one of the practical reason to support the former results [41]. Based on the data from Diabetes Canada, another reason can be highlighted which is the income differences between rural and urban individuals. The prevalence of diabetes among adults with the lowest income is almost 5 times higher than among adults with the relatively highest income in Canada [42]. The education level is also playing a significant role, which is supported by the data that adults without a high school degree have 5.2 times more likely tend to develop type 2 diabetes than those with a university education [42].

From the perspective of the whole world, the Pima Indians as an ethnic group have a congenital disability with relatively the highest risk of developing type 2 diabetes mellitus (especially among Arizona Pimas aged older than 35 years old) should be highlighted [47]. They must be performed more attention based on their history, living environment, behaviors, and results from previous studies. The Pima are normally known as both Mexican and Arizona types, but they mostly have the same nutrient intakes. Hunting mule deer, jackrabbits and birds, fishing from the Gila River, and gathering food from the desert were the major food resources [43]. Because of their old living environment around the desert, the "thrifty gene" hypothesis majorly states that populations who have struggled with periods of limited resources and have experienced famine were more likely to survive if they were metabolically thrifty and stored calories efficiently. The privilege seems to bring Pima Indians many more benefits, but it is not well-fitted in our current modern environment. Their "thrifty gene" may become a crucial risk factor for their extremely high risk for type 2 diabetes mellitus and obesity. Compared to Arizona Pimas, the Mexican Pimas live around the small town of Maycoba in the Mexican state with their food on sloped fields with an extremely high physical activity because of their labor-intensive lifestyle [42]. All Mexican groups had significantly higher physical activity levels (2.5 times greater) than the Arizona Pima population under gender and age standardiza-

tions [42]. Unlike the Mexican Pimas who had no outside factors to change their living behaviors, Arizona Pima's environment is modern with high dietary fat intake, low physical activity, and a sedentary lifestyle, which triggers a significantly higher opportunity to develop type 2 diabetes mellitus [42]. A well-organized paper by Ling and Ronn supports the hypothesis that environmental changes may activate or inactivate specific genes for type 2 diabetes mellitus and obesity [44]. The authors mentioned that the abundance of fast food and other high-energy resources and low physical activity lifestyle linked to altered gene activity, and hence the link between rapid changes in eating habits and the observed obesity phenotype [44]. Other potential risk factors such as leptin level and insulin resistance in Pimas are still under investigation. Environmental change from traditional to more modern acts as a dominant factor to impact the Pimas, especially Mexican Pimas' lifestyle over the decades, showing modernization is a double-side sword that improves the quality of life. However, it has a high potential to promote unhealthy life.

Gingivitis and Periodontitis in Diabetic-Patients

Gingivitis

Gingivitis is a common and mild form of periodontal disease that results in irritation, redness, and inflammation of the gingiva, the tissues that cover around the base of the teeth. Compared to healthy gums colored in light pink and well-fitted around the teeth, individuals with gingivitis have puffy, dark red gums which bleed easily while brushing. People, especially children and youth adults with a high risk of developing type 1 diabetes, are at greater risk of developing gingivitis. In addition, studies have shown that poor metabolic control in children and adults is associated with a higher prevalence of gingivitis [45]. Prevalence of gingivitis in diabetic children and adolescents is twice higher than in those without diabetes, showing that diabetes dominantly increases the severity and extent of gingivitis among young patients [45]. The rate of gingiva inflammation in type 2 diabetic adults is higher than those in non-diabetic adults.

Periodontitis

Unlike gingivitis, periodontitis, a more irreversible severe form of gingivitis, is an infection around the periodontium which supports the tooth against oral microflora. The main cause of this condition is bacterial infection leading to an increase in microbiome diversity and replacement and loss of keystone species, resulting in the accumulation of plaques on the teeth and hardening. Under this condition, permanent bad breath, red or swollen and bleeding gums, black plaques, and loose and sensitive teeth can be seen in the patients. Furthermore, the gums can pull away from the tooth, causing bone loss, and the teeth may loosen or even fall out (attachment loss) depending on its duration on the human body. Periodontitis is typically seen in adults, but it is uncommon in children younger than 12 years or even among those individuals with diabetes. Even though periodontitis does appear in adolescence, attachment loss is not always at a severe level [46]. Individuals aged 35 years old and older with more than 10-year type 1 diabetes had a more severe degree of periodontal attachment loss than those with

less than 10-year type 1 diabetes mellitus [47]. In addition, Glavind *et al.* demonstrated that patients with type 1 diabetes who developed other diabetes-related complications have significantly worse attachment loss than those without complications experience [47]. Once one of the diabetes-related complications occurs, patients are more likely to develop additional chronic complications as the condition grows [47] [48] [49].

Bidirectional relationship between Diabetes and Periodontitis

Impact of diabetes on periodontal status

The function of neutrophils, monocytes, and macrophages is altered in diabetic patients [50]. Neutrophils are the principal mediators of the quick innate hose response against the majority of bacterial and fungal pathogens that occurs prior to the complicated humoral and lymphocyte cellular processes of acquired immunity during infection. Dowey *et al.* emphasized that Not only is glucose an enhanced pro-inflammatory mediator in type 1 diabetes mellitus and type 2 diabetes mellitus [51]. Insulin insufficiency and resistance change lipid metabolism, increasing lipogenesis and adipose tissue metabolism. Lipids and neutrophils have been demonstrated to upregulate critical pro-inflammatory neutrophil capabilities such as cytokine synthesis and ROS (reactive oxygen species) production [51]. Due to exposure to the diabetic milieus, which includes changes in blood glucose levels as well as other variables, neutrophil activity is changed in diabetes (**Figure 5**) [51]. Recruitment, chemotaxis, phagocytosis, and intracellular ROS production, which are essential neutrophil pathways involved in response to infection, are all impaired in diabetes, but pro-inflammatory cytokine production, extracellular

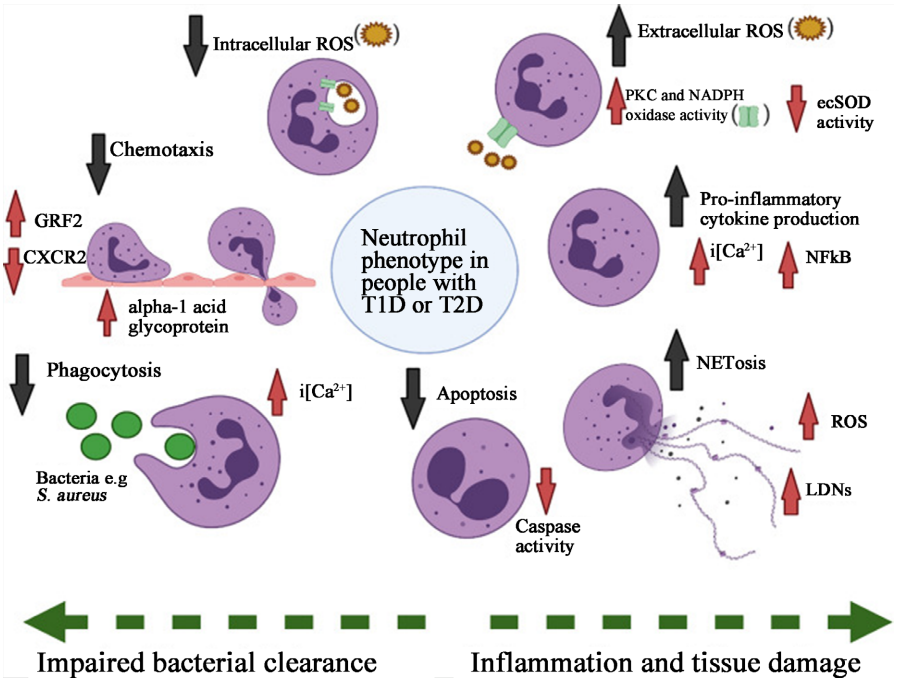


Figure 5. A summary of altered functions of neutrophils in T1D and T2D patients. Created by Dowey *et al.*, 2021 [51].

ROS production, cell survival, and the formation of neutrophil extracellular traps are upregulated and are now recognized as essential mediators of diabetic complications [51].

Monocytes and macrophages are crucial in the immune system, functioning in phagocytosis, antigen presentation, and cytokine production, resolving inflammation, and facilitating wound repair [52]. Within the high-glucose environment created by diabetic patients, the functions of former immune cells will be altered or inhibited, which may prevent the destruction of bacteria in the periodontal pocket, leading to periodontal destruction [50]. As the damage occurred, fibroblast will not function properly in a high-glucose environment. Thus, periodontal wound healing may be impaired, causing cumulative damage within the oral cavity if no appropriate treatment is involved. There is a significant influence for diabetic patients with poor glycemic control on oral health because of the accumulated high levels of glycated proteins (HbA1c). As the most prevalent protein in the body, collagen becomes glycated under a high-glucose environment creating AGE-enriched gingival tissue by accumulating advanced glycated end products (AGEs) in the periodontium. Interactions between AGEs and their receptors (RAGEs) will further result in decreased collagen production, negatively impacting wound healing. AGE-enriched gingival tissues impact the risk and rate of periodontal diseases [50]. The risk and rate of periodontal disease are impacted by such tissues, and advanced systemic complications increase the frequency and severity of periodontists in diabetic patients [50].

Effects of periodontitis on diabetes

Not only diabetes is a risk factor for periodontitis, but periodontitis also has a negative effect on some of the pathway that increases the incidence of diabetes. The main driver of periodontitis is the periodontal bacteria and their products which trigger immune cells and other mediators found in the infected periodontal tissues. Those molecules enter the human circulating system and upregulate systemic inflammation. As a result, a reduction of insulin-mediated uptake in skeletal muscles leads to impaired insulin signaling, abnormal insulin resistance, poor glycemic control, and eventually increases the risk of diabetes. The specific mechanisms in the effects of periodontitis on diabetes are underlying, but chronic periodontal disease can exacerbate insulin resistance and worsen glycemic control and leading to long-term diabetic complications.

4. Discussion

The increased systemic infections and inflammation caused by periodontitis encourage insulin resistance, resulting in type 2 diabetes mellitus and further developing diabetes-related complications. As periodontitis can be cumulative, for patients with pre- and diabetes is mandatory to check their oral status and discuss with oral health care practitioners to develop a treatment against potential infection and inflammation. In order to examine the risk factors for periodontal disease and ascertain the actual state of the gums, teeth, and underlying jawbone,

the dentist will utilize the patient's medical history, family history, and dental X-rays by cooperating with other healthcare practitioners to access shared practical data. Sufficient periodontal therapy, including scaling and root planning, localized gingivectomy, selected tooth extraction, and antibiotic, influence glycemic control with decreased HbA1c levels and reduces inflammation [50]. Chronic periodontal disease may exacerbate insulin resistance and worsen glycemic control. Appropriate periodontal treatment decreases inflammation leading reducing insulin resistance. Dentists play an indispensable role in providing timely advice to patients with types of diabetes and assist them in practicing good self-care, which includes using an antiseptic mouthwash and dentifrice twice daily, flossing once daily, and using interproximal aids. The positive impact of periodontal therapy on diabetic patients' metabolic management is an example of the potential benefit of a deeper comprehension of the link between these illnesses and of the practical implementation of the ideas of biological plausibility.

5. Conclusions

This review study may have some limitations, which may affect the reliability, precision, and validity. The first is some published data mentioned above and selected from previous studies, and released reports are relatively early due to no permission to access the latest data. This issue can be solved and needed to double-check with governments and other professional organizations in the future. The second limitation concerns the suggestion of dentists' roles in treating diabetic or prediabetic patients via periodontal treatment and other dental treatments due to the lack of previous research studies on the topic.

Diabetes is a complex disease affected by numerous risk factors that can trigger the further development of its related complications, especially periodontitis. It significantly impacts many body tissues, including the oral cavity. Many poorly controlled behaviors are highly related to the increase in the prevalence of periodontitis under diabetic conditions. After understanding the bidirectional relationship between periodontal disease and diabetes mellitus, inflammation is the common link caused by a combination of many factors. With a thorough understanding of the relationship between oral health and overall wellness, dentists can provide purposeful treatments to prevent or reduce the risk of periodontal disease and diabetes based on much information, including the patients' ethnicity, history of physical condition, behaviors, and lifestyle.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] World Health Organization (2023) Diabetes. https://www.who.int/health-topics/diabetes#tab=tab_1

[2] Keays, R. (2007) Diabetes. *Current Anaesthesia and Critical Care*, **18**, 69-75. https://doi.org/10.1016/j.cacc.2007.03.007

[3] Bascones-Martínez, A., González-Febles, J. and Sanz-Esporrín, J. (2014) Diabetes and Periodontal Disease. Review of the Literature. *American Journal of Dentistry*, **27**, 63-67.

[4] Public Health Agency of Canada (2009) Report from the National Diabetes Surveillance System: Diabetes in Canada. PHAC, Ottawa, 6.

[5] Public Health Agency of Canada (PHAC) (2011) Fast Facts about Diabetes: Data Compiled from the 2011 Survey on Living with Chronic Diseases in Canada. PHAC, Ottawa. https://www.canada.ca/en/public-health/services/chronic-diseases/reports-publications/diabetes/fast-facts-about-diabetes-2011.html

[6] (n.d.) Diabetes Rates Continue to Climb in Canada. https://www.diabetes.ca/media-room/press-releases/diabetes-rates-continue-to-climb-in-canada

[7] (n.d.) Diabetes in Canada. https://www.diabetes.ca/advocacy---policies/advocacy-reports/national-and-provincial-backgrounders/diabetes-in-canada

[8] (2020) Diabetes in Canada: Backgrounder. Diabetes Canada, Ottawa. https://www.diabetes.ca/DiabetesCanadaWebsite/media/Advocacy-and-Policy/Backgrounder/2020_Backgrounder_Canada_English_FINAL.pdf

[9] (n.d.) Diabetes in Ontario. https://www.diabetes.ca/advocacy---policies/advocacy-reports/national-and-provincial-backgrounders/diabetes-in-ontario

[10] Public Health Toronto (2017) Health Surveillance Indicator: Diabetes. https://www.toronto.ca/wp-content/uploads/2017/12/8c72-tph-hsi-diabetes-july18f.pdf

[11] Diabetes in Canada: Facts and Figures from a Public Health Perspective. Public Health Agency of Canada, Ottawa, 126. https://www.diabetes.ca/advocacy---policies/advocacy-reports/national-and-provincial-backgrounders/diabetes-in-canada

[12] Deshpande, A.D., Harris-Hayes, M. and Schootman, M. (2008) Epidemiology of Diabetes and Diabetes-Related Complications. *Physical Therapy*, **88**, 1254-1264. https://doi.org/10.2522/ptj.20080020

[13] National Center for Health Statistics, Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES). http://www.cdc.gov/nchs/nhanes.htm

[14] Hux, J., Booth, J., Slaughter, P. and Laupacis, A. (2003) Diabetes in Ontario: An ICES Practice Atlas. Institute for Clinical Evaluative Sciences.

[15] Robinson, D.J., Coons, M., Haensel, H., Vallis, M. and Yale, J.-F. (2018) Diabetes and Mental Health. *Canadian Journal of Diabetes*, **42**, S130-S141. https://doi.org/10.1016/j.jcjd.2017.10.031

[16] Singh, N., Armstrong, D.G. and Lipsky, B.A. (2005) Preventing Foot Ulcers in Patients with Diabetes. *JAMA*: *The Journal of the American Medical Association*, **293**, 217-228. https://doi.org/10.1001/jama.293.2.217

[17] Löe, H. (1993) Periodontal Disease. The Sixth Complication of Diabetes Mellitus. *Diabetes Care*, **16**, 329-334. https://doi.org/10.2337/diacare.16.1.329

[18] Tan, S.Y., Mei Wong, J.L., Sim, Y.J., *et al.* (2019) Type 1 and 2 Diabetes Mellitus: A Review on Current Treatment Approach and Gene Therapy as Potential Intervention. *Diabetes & Metabolic Syndrome*, **13**, 364-372.

https://doi.org/10.1016/j.dsx.2018.10.008

[19] Wilcox, G. (2005) Insulin and Insulin Resistance. *The Clinical Biochemist. Reviews*, **26**, 19-39.

[20] Diabetes Canada Clinical Practice Guidelines Expert Committee (2018) Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Canadian Journal of Diabetes*, **42**, S1-S325. https://doi.org/10.1016/S1499-2671(17)31026-2

[21] Singh, N., Kesherwani, R., Tiwari, A.K. and Patel, D.K. (2016) A Review on Diabetes Mellitus. *The Pharma Innovation*, **5**, 36-40. https://www.thepharmajournal.com/archives/?year=2016&vol=5&issue=7&ArticleId=811

[22] Yoon, J. and Jun, H.-S. (2005) Autoimmune Destruction of Pancreatic β Cells. *American Journal of Therapeutics*, **12**, 580-591. https://doi.org/10.1097/01.mjt.0000178767.67857.63

[23] Ismail, L., Materwala, H. and Al Kaabi, J. (2021) Association of Risk Factors with Type 2 Diabetes: A Systematic Review. *Computational and Structural Biotechnology Journal*, **19**, 1759-1785. https://doi.org/10.1016/j.csbj.2021.03.003

[24] Niskanen, L., Laaksonen, D.E., Lindström, J., Eriksson, J.G., Keinänen-Kiukaanniemi, S., Ilanne-Parikka, P. and Uusitupa, M. (2006) Serum Uric Acid as a Harbinger of Metabolic Outcome in Subjects with Impaired Glucose Tolerance: The Finnish Diabetes Prevention Study. *Diabetes Care*, **29**, 709-711. https://doi.org/10.2337/diacare.29.03.06.dc05-1465

[25] Dehghan, A., van Hoek, M., Sijbrands, E.J.G., Hofman, A. and Witteman, J.C.M. (2008) High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. *Diabetes Care*, **31**, 361-362. https://doi.org/10.2337/dc07-1276

[26] Chien, K.-L., Chen, M.-F., Hsu, H.-C., Chang, W.-T., Su, T.-C., Lee, Y.-T. and Hu, F.B. (2008) Plasma Uric Acid and the Risk of Type 2 Diabetes in a Chinese Community. *Clinical Chemistry*, **54**, 310-316. https://doi.org/10.1373/clinchem.2007.095190

[27] Nan, H., Qiao, Q., Söderberg, S., Pitkäniemi, J., Zimmet, P., Shaw, J. and Tuomilehto, J. (2008) Serum Uric Acid and Incident Diabetes in Mauritian Indian and Creole Populations. *Diabetes Research and Clinical Practice*, **80**, 321-327. https://doi.org/10.1016/j.diabres.2008.01.002

[28] Zizi, F., Jean-Louis, G., Brown, C.D., Ogedegbe, G., Boutin-Foster, C. and McFarlane, S.I. (2010) Sleep Duration and the Risk of Diabetes Mellitus: Epidemiologic Evidence and Pathophysiologic Insights. *Current Diabetes Reports*, **10**, 43-47. https://doi.org/10.1007/s11892-009-0082-x

[29] Shoelson, S.E., Lee, J. and Goldfine, A.B. (2006) Inflammation and Insulin Resistance. *The Journal of Clinical Investigation*, **116**, 1793-1801. https://doi.org/10.1172/JCI29069

[30] Hayashino, Y., Fukuhara, S., Suzukamo, Y., Okamura, T., Tanaka, T., Ueshima, H. and HIPOP-OHP Research Group (2007) Relation between Sleep Quality and Quantity, Quality of Life, and Risk of Developing Diabetes in Healthy Workers in Japan: The High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. *BMC Public Health*, **7**, Article No. 129. https://doi.org/10.1186/1471-2458-7-129

[31] Mallon, L., Broman, J.-E. and Hetta, J. (2005) High Incidence of Diabetes in Men with Sleep Complaints or Short Sleep Duration: A 12-Year Follow-Up Study of a Middle-Aged Population. *Diabetes Care*, **28**, 2762-2767.

https://doi.org/10.2337/diacare.28.11.2762

[32] (2022) Tobacco. https://www.who.int/news-room/fact-sheets/detail/tobacco

[33] Bajaj, M. (2012) Nicotine and Insulin Resistance: When the Smoke Clears. *Diabetes*, **61**, 3078-3080. https://doi.org/10.2337/db12-1100

[34] Will, J.C., Galuska, D.A., Ford, E.S., Mokdad, A. and Calle, E.E. (2001) Cigarette Smoking and Diabetes Mellitus: Evidence of a Positive Association from a Large Prospective Cohort Study. *International Journal of Epidemiology*, **30**, 540-546. https://doi.org/10.1093/ije/30.3.540

[35] Wannamethee, S.G., Shaper, A.G., Perry, I.J. and British Regional Heart Study (2001) Smoking as a Modifiable Risk Factor for Type 2 Diabetes in Middle-Aged Men. *Diabetes Care*, **24**, 1590-1595. https://doi.org/10.2337/diacare.24.9.1590

[36] Kowall, B., Rathmann, W., Strassburger, K., Heier, M., Holle, R., Thorand, B. and Meisinger, C. (2010) Association of Passive and Active Smoking with Incident Type 2 Diabetes Mellitus in the Elderly Population: The KORA S4/F4 Cohort Study. *European Journal of Epidemiology*, **25**, 393-402. https://doi.org/10.1007/s10654-010-9452-6

[37] Cho, N.H., Chan, J.C.N., Jang, H.C., Lim, S., Kim, H.L. and Choi, S.H. (2009) Cigarette Smoking Is an Independent Risk Factor for Type 2 Diabetes: A Four-Year Community-Based Prospective Study. *Clinical Endocrinology*, **71**, 679-685. https://doi.org/10.1111/j.1365-2265.2009.03586.x

[38] Foy, C.G., Bell, R.A., Farmer, D.F., Goff, D.C. and Wagenknecht, L.E. (2005) Smoking and Incidence of Diabetes among U.S. Adults: Findings from the Insulin Resistance Atherosclerosis Study. *Diabetes Care*, **28**, 2501-2507. https://doi.org/10.2337/diacare.28.10.2501

[39] Manson, J.E., Ajani, U.A., Liu, S., Nathan, D.M. and Hennekens, C.H. (2000) A Prospective Study of Cigarette Smoking and the Incidence of Diabetes Mellitus among US Male Physicians. *The American Journal of Medicine*, **109**, 538-542. https://doi.org/10.1016/S0002-9343(00)00568-4

[40] Suastika, K., Dwipayana, P., Siswadi, M. and Tuty, R.A. (2012) Age Is an Important Risk Factor for Type 2 Diabetes Mellitus and Cardiovascular Diseases. In: Chackrewarthy, S., Ed., *Glucose Tolerance*, InTech, London, 67-80. https://doi.org/10.5772/52397

[41] Zimmet, P., Faaiuso, S., Ainuu, J., Whitehouse, S., Milne, B. and DeBoer, W. (1981) The Prevalence of Diabetes in the Rural and Urban Polynesian Population of Western Samoa. *Diabetes*, **30**, 45-51. https://doi.org/10.2337/diab.30.1.45

[42] Pan-Canadian Health Inequalities Data Tool, 2017 Edition (n.d.). https://nccdh.ca/resources/entry/pan-canadian-health-inequalities-data-tool-2017-edition

[43] Schulz, L.O. and Chaudhari, L.S. (2015) High-Risk Populations: The Pimas of Arizona and Mexico. *Current Obesity Reports*, **4**, 92-98. https://doi.org/10.1007/s13679-014-0132-9

[44] Ling, C. and Rönn, T. (2019) Epigenetics in Human Obesity and Type 2 Diabetes. *Cell Metabolism*, **29**, 1028-1044. https://doi.org/10.1016/j.cmet.2019.03.009

[45] Ryan, M.E., Carnu, O. and Kamer, A. (2003) The Influence of Diabetes on the Periodontal Tissues. *Journal of the American Dental Association* (1939), **134**, 34S-40S. https://doi.org/10.14219/jada.archive.2003.0370

[46] Jenkins, W.M. and Papapanou, P.N. (2001) Epidemiology of Periodontal Disease in Children and Adolescents. *Periodontology*, **26**, 16-32. https://doi.org/10.1034/j.1600-0757.2001.2260102.x

[47] Glavind, L., Lund, B. and Löe, H. (1968) The Relationship between Periodontal State and Diabetes Duration, Insulin Dosage and Retinal Changes. *Journal of Periodontology*, **39**, 341-347. https://doi.org/10.1902/jop.1968.39.6.341

[48] Rosenthal, I.M., Abrams, H. and Kopczyk, A. (1988) The Relationship of Inflammatory Periodontal Disease to Diabetic Status in Insulin-Dependent Diabetes Mellitus Patients. *Journal of Clinical Periodontology*, **15**, 425-429. https://doi.org/10.1111/j.1600-051X.1988.tb01596.x

[49] Cullinan, M., Ford, P. and Seymour, G. (2009) Periodontal Disease and Systemic Health: Current Status. *Australian Dental Journal*, **54**, S62-S69. https://doi.org/10.1111/j.1834-7819.2009.01144.x

[50] Ryan, M.E. (2013, July 17) Complex Connection. https://dimensionsofdentalhygiene.com/article/complex-connection https://doi.org/10.7312/columbia/9780231163842.003.0001

[51] Dowey, R., Iqbal, A., Heller, S.R., Sabroe, I. and Prince, L.R. (2021) A Bittersweet Response to Infection in Diabetes; Targeting Neutrophils to Modify Inflammation and Improve Host Immunity. *Frontiers in Immunology*, **12**, Article ID: 678771. https://doi.org/10.3389/fimmu.2021.678771

[52] Kratofil, R.M., Kubes, P. and Deniset, J.F. (2017) Monocyte Conversion during Inflammation and Injury. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **37**, 35-42. https://doi.org/10.1161/ATVBAHA.116.308198