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Periodontal disease severity-correlation with diabetes and obesity measures?

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**PERIODONTAL DISEASE SEVERITY-CORRELATION WITH DIABETES AND
OBESITY MEASURES?**

by

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ABSTRACT

This paper studies the correlation between three widely common chronic diseases, periodontal disease, diabetes, and obesity. The three diseases share one key factor; they not only affect human's health but also the style and quality of life. This paper evaluated the current literature regarding periodontal disease, diabetes, obesity, and their triangular relationship. The studies showed that the three chronic diseases are related to each other in a triangular relationship. Increased adiposity manifested by BMI greater than 30, leads to increased systemic inflammation through the release of inflammatory adipokines from the fatty deposits, this leads to the development of diabetes mellitus by different mechanisms, partly by destruction of the islet cells of Langerhans and partly by insulin resistance. One of the complications of diabetes mellitus is periodontal disease, which is a list of clinical conditions that adversely affect the health of the periodontium. Moreover, current literature provides evidence that the relationship between diabetes and periodontal disease is bidirectional. Evidence from current studies is showing that periodontal disease might lead to the development of diabetes by increasing the systemic inflammation, this occurs by the invasion of periodontal pathogens of the endothelial cells where they elicit an exacerbated systemic inflammation which

might lead to the development of diabetes and other chronic conditions. This paper shows the importance of collaborative work between the dental and the medical professionals to ensure the overall health of an individual. Primary care physicians are encouraged to refer patients with poor glycemic control to dentists for an assessment of the health of their oral cavity and vice versa; dentists should be more aware of the systemic complications of oral diseases and should educate their patients about such relationships.

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LIST OF ABBREVIATIONS

ADA	American Dental Association
AGE	Advanced Glycation End products
APCs	Antigen Presenting Cells
BMI	body mass index
CDC	Center for Disease Control and Prevention
DM	Diabetes Mellitus
DM	Diabetes Mellitus
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
FFA	free fatty acids
GLUT-2	Glucose transporter 2
HAEC	human aortic endothelial cells
HDL	high-density cholesterol
HUVEC	human umbilical vein endothelial cells
ICAM	intracellular adhesion molecule
IL	Interleukin
iNOS	inducible nitric oxide synthase
MCP	monocyte chemoattractant protein
NIDDK	National Institute of Diabetes, Digestive and Kidney Disease

NO	nitric oxide
P	<i>Porphyromonas</i>
RAGE	Receptor for Advanced Glycation End products
ROS	reactive oxygen species
TG	triglyceride
TNF- α	Tumor Necrosis Factor alpha
VCAM	vascular cellular adhesion
VLDL	very low density lipoproteins
WC	waist circumference
WHO	World Health Organization
WHO	World Health Organization

INTRODUCTION

Diabetes is a widely common systemic morbidity in today's world in both developing and developed nations. Recently many studies have investigated not only the role of obesity in diabetes but also if a causative correlation exists between obesity, diabetes and the progression of periodontal disease. This study aims to provide evidence for an underlying mechanism linking diabetes, obesity and periodontal disease.

Diabetes

Diabetes Mellitus (DM) is a global epidemic whose complications impact the quality of life significantly (Figure 1) (1). Moreover, diabetes affects longevity and health care costs (2). Diabetes is one of the top ten leading causes of death in most world-wide (Figure 2) and the 7th in developed countries and it is an endemic in many developing and newly industrialized nations (3).

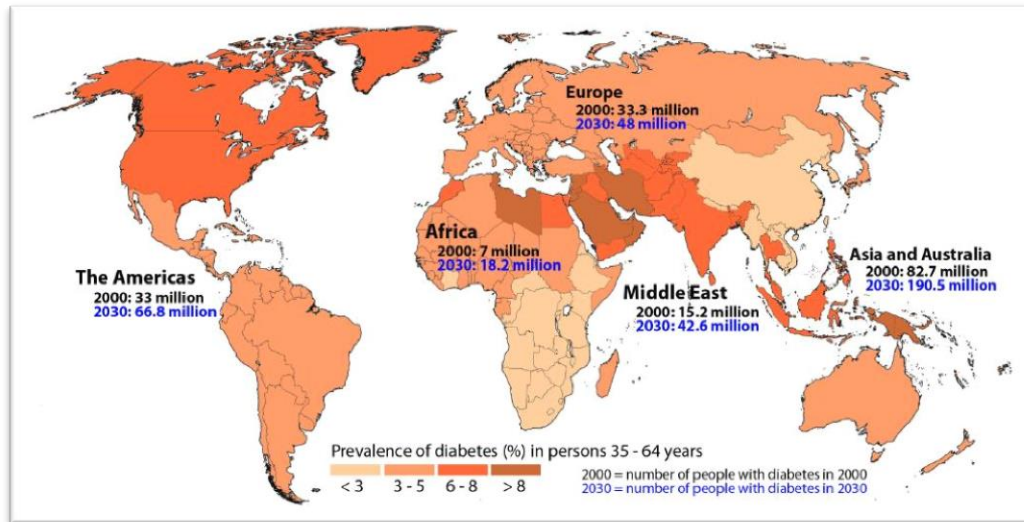


Figure 1: Prevalence of Diabetes World-Wide. Shown is the prevalence relative to population and morbidity levels for 2000 and projected for 2030. Figure downloaded from Globalist Report (1).

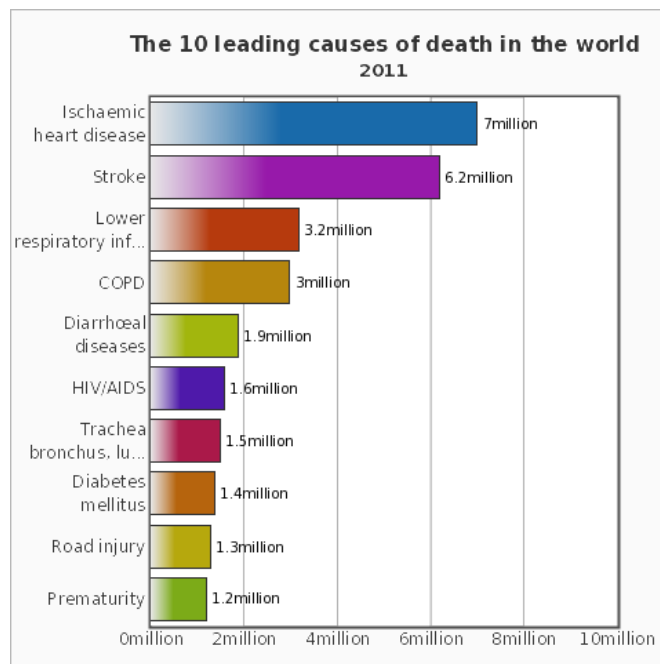


Figure 2: Prevalence of Diabetes World-Wide. Shown is the prevalence for 2011. Figure downloaded from WHO International – The Top 10 Causes of Death (2).

The World Health Organization (WHO) predicts there will be an increase in the number of people with diabetes from 347 to 439 million by 2030 (4). In the United States, 8.3% of the population has diabetes including 25.8 million children and adults. There are 215,000 people under the age of 20 have diabetes; about 1 in every 400 children or adolescents has diabetes, 25.6 million people who are 20 and older have it and 10.9 million people who are 65 or older have it. The total number of men and women with diabetes is 13 million and 12.6 million respectively (5).

There are important differences in the prevalence of diabetes among different races and ethnicities; diabetes affects 7.1% of non-Hispanic whites, 8.4% of Asian Americans, 12.6% of non-Hispanic blacks, 11.8% of Hispanics. Among Hispanics rates were, 7.6% for Cubans, 13.3% for Mexican Americans, and 13.8% for Puerto Ricans (Figure 3)(6) . This escalating problem necessitates the development of preventive and therapeutic measures to manage this growing disease and its complications. Diabetes is preceded by an inflammation in the body, which will eventually lead to the apoptosis of pancreatic beta cells, and the development of insulin resistance (7). Therefore any condition that contributes to systemic inflammation (for example obesity) will exacerbate the complications of diabetes.

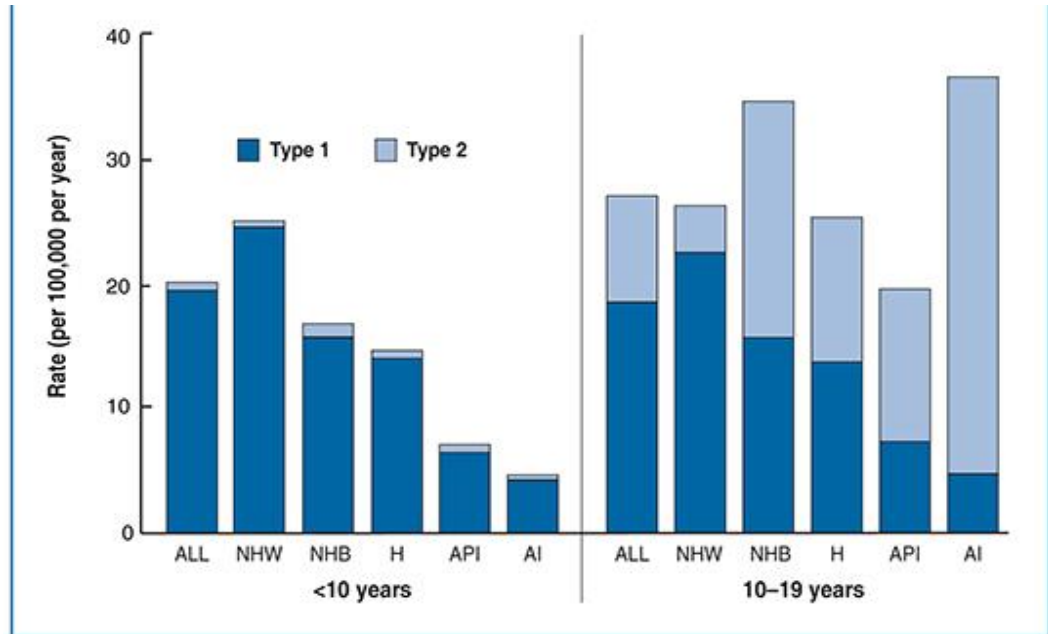


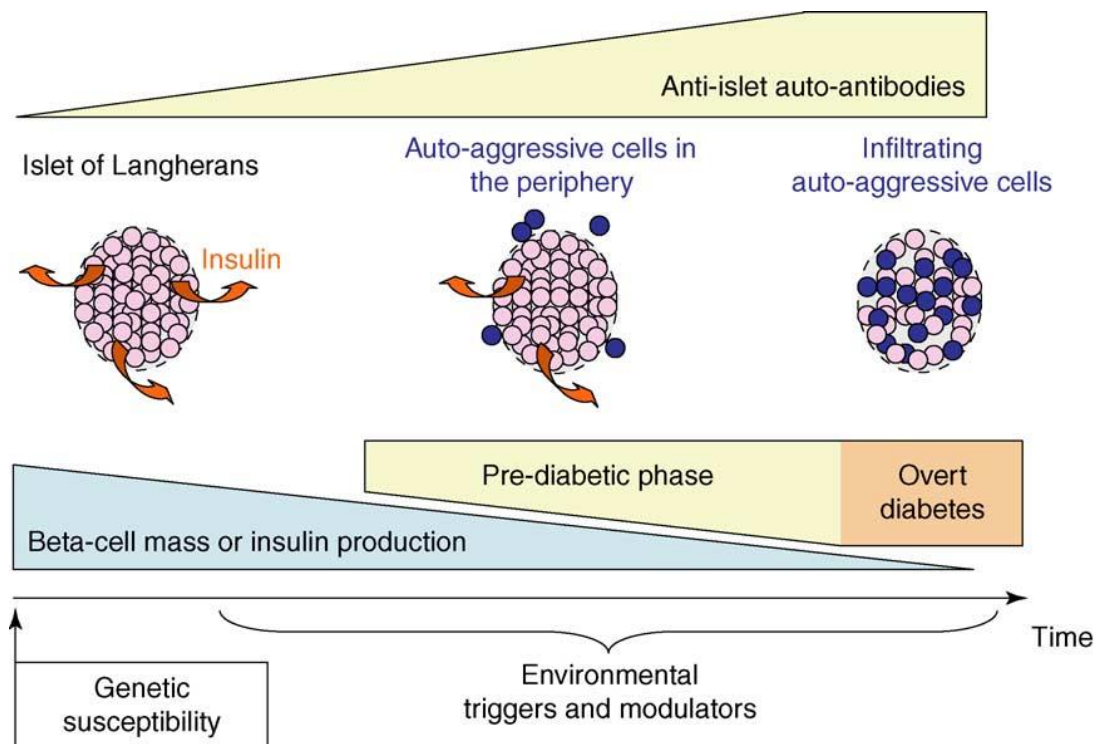
Figure 3: New Cases of Type 1 and Type 2 Diabetes among Youth Younger than 20 Years Old from 2002-2005. Shown is the rate of new cases by race and ethnicity among the following groups: NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics/Latinos; API=Asian/Pacific Islander Americans; AI=American Indians. Figure taken from NIDDK- National Diabetes Statistics 2011 (7).

DM is a metabolic disease that is characterized by high blood glucose levels due to insufficient amount of insulin secreted by beta cells or due to insulin resistance in which insulin target cells do not respond to the insulin produced (8). DM has many symptoms including polyuria which is frequent urination, polydipsia or excessive thirst, unexplained weight loss, polyphagia which is extreme hunger, sudden vision changes, tingling or numbness in the hands or feet, feeling very tired much of the time, very dry skin, sores that are slow to heal, more infections than

usual. Some people may experience some of the symptoms listed above but others might not experience any and might not know they are diabetic until their blood sugar reaches very high levels (9).

There are three main types of DM, Type 1 which was previously called juvenile DM and is insulin dependent. Type 1 DM is usually diagnosed in children and young adults, only 5% of the total diagnosed people with diabetes have Type 1 (10). Patients with this type of DM do not produce insulin which is necessary for glucose uptake into the cells. It is also classified as an autoimmune disease, as it occurs through activation of auto-aggressive T cells that are thought to mediate destruction of beta cells in the pancreas. Thus insulin is no longer secreted, it is multi-factorial involving a genetic predisposition [11] and environmental triggers [12] such as viruses. Several studies have shown the concordance rate for the development of Type I DM among monozygotic twins is no more than 50% which shows that Type I DM is not exclusively genetic and that other factors can come into play. Although imperfectly understood, environmental challenges may contribute to accelerating or triggering autoimmune diseases in genetically predisposed people (13). Many studies showed that viral infections are powerful events in triggering Type 1 DM, they do this by breaking the tolerance against self antigens so the body starts destroying its own cells. This occurs by three different mechanisms: (i) by inducing virus-mediated cell damage of target organs directly or via secretion of inflammatory cytokines that specifically harm beta cells, (ii) by enhancing function

of antigen presenting cells (APCs) leading to increased presentation of autoantigens and/or (iii) by molecular mimicry, where immunity against viral antigens cross-reacts with self-antigens that are exhibiting a conformationally similar structure (14). Evidence from several mouse and human models show that Type I DM is a T-cell mediated autoimmune disease. From autopsies of pancreata of patients who recently died from sudden onset of Type I DM it was demonstrated that there was an infiltration of lymphocytes and macrophages with high proportion of CD8+ cells, which are a type of cytotoxic T cells that destroy virally infected and tumor cells. They express the CD 8 glycoprotein on their surface (15). A schematic illustrating the pathogenesis of Type I DM is shown below in Figure 4.



Drug Discovery Today: Disease Mechanisms

Figure 4. Pathogenesis of Type 1 Diabetes Mellitus. Schematic model showing infiltration and destruction of the islets of Langerhans over the time. At least three factors might be involved in the destruction of beta cells. Genetic susceptibility is required to create a fertile environment for T1D development, several environmental factors might trigger the pathogenesis and precipitate the pre-diabetic phase (factor 2). Lastly, destruction of insulin-producing beta cells by sufficient numbers of infiltrating autoaggressive T cells leads to overt diabetes (factor 3). Counter-regulation of autoaggression by autoreactive regulatory T cells might be capable of preventing destruction of all beta cells even late during disease. Figure taken from *Drug Discovery Today: Disease Mechanisms* (12).

Type II DM is characterized by hyperglycemia, insulin resistance and relative insufficient insulin secretion (Figure 5). The fact that it is a genetic disease was known to clinicians a long time ago, but a genetic predisposition is not the only cause of Type II DM (16). Our current life style has definitely a great deal to do with it, the high calorie intake, and the low expenditure of energy along with the sedentary life style is all leading to the development of diabetes through obesity, which will be further explained later on in the paper. Understanding the pathological mechanism of development Type II DM is a complex process but Type II diabetic patients usually present varying degrees of insulin resistance and insulin deficiency and it is usually the combination of both that lead to the development of the disease. Insulin secretion by beta cells requires glucose transport into the cell, which is at least in part mediated by the glucose transporter 2 (GLUT-2). A mouse model with a genetic alteration affecting GLUT-2 expression produced mice with glucose intolerance; similar changes in GLUT-2 could be induced in normal mice fed a high-fat diet (17) and suggests a possible mechanism for the link between high-fat diet and the development of diabetes. Impaired insulin secretion in mice was also shown in those that lack Abca1, which is a cellular cholesterol transporter. Mice with inactivated Abca 1 in their beta cells have defective insulin secretion and impaired glucose tolerance (18).

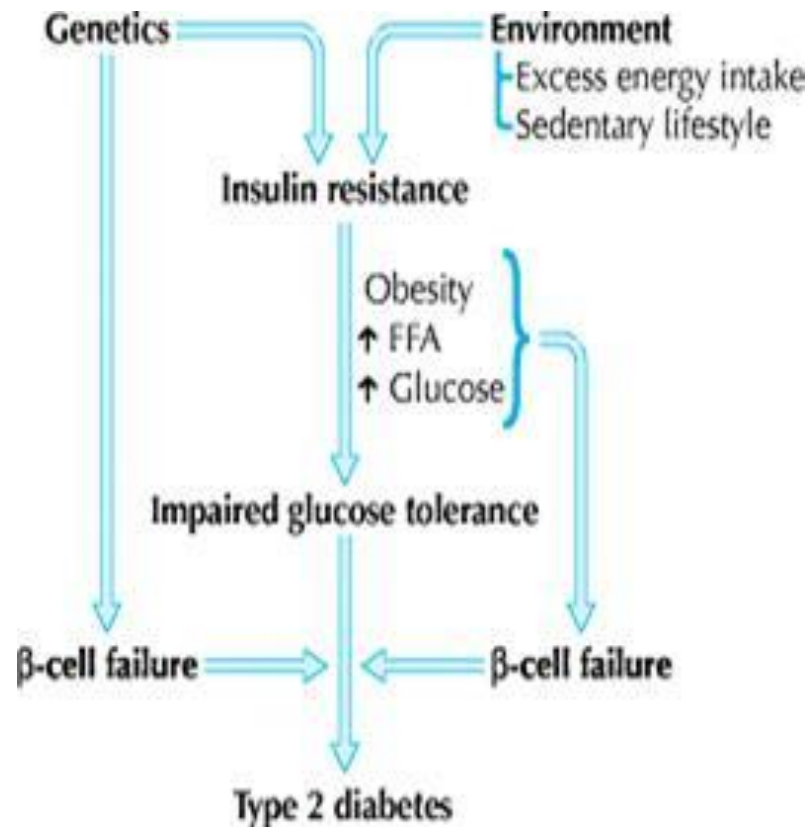


Figure 5: Pathogenesis of Type 2 Diabetes Mellitus Shown is a schematic demonstrating the pathogenesis of DM and its predisposition with respect to genetic and environmental factors. Figure taken from Greevenbroek et al., 2013 (7).

People with Type 2 diabetes often have no symptoms at first. They may not have symptoms for many years. Early symptoms of diabetes may include: bladder, kidney, skin, or other infections that are more frequent or heal slowly, fatigue, hunger, increased thirst, increased urination, the first symptom may also be; blurred vision, erectile dysfunction, pain or numbness in the feet or hands (19). The goal of treatment of Type II diabetes is to lower the blood glucose levels and in the long term to prevent any complications that may arise from diabetes, like blindness,

amputations due to gangrenes and kidney disease (20). The most important way to treat and manage Type II diabetes is nutrition, weight management and activity. Diabetics need to check their blood glucose level regularly or at least twice a day, they should know what to eat and when to eat it and if nutrition, activity and weight control fail to drop their blood glucose levels down, they can take medications like alpha-glucosidase inhibitors, biguanides, DPP IV inhibitors, injectable medicines, meglitinides, sulfonylureas and thiazolidinediones (21).

Obesity

Obesity is one of the major risk factors for diabetes besides genetic predisposal (22). Worldwide, at least 2.8 million people die from associated conditions each year as a result of being overweight or obese, and an estimated 35.8 million (2.3%) globally (23). Overweight and obesity are defined according to the WHO (World Health Organization) as excessive or abnormal fat accumulation that affects an individual's health negatively (24). Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer and while it was once an issue only in high-income countries, overweight and obesity has now dramatically risen in low- and middle-income countries (25). Such countries are now facing a "double burden" of disease, for while they continue to deal with the problems of infectious disease and under-nutrition, they are also experiencing a rapid upsurge in chronic disease risk factors such as obesity and

overweight, particularly in urban settings. Obesity is measured by the BMI which is weight to height ratio, it is the person's weight in Kilograms divided by the square height in meters (Figure 6) (26).

The WHO defines an adult who has a BMI between 25 and 29.9 as overweight - an adult who has a BMI of 30 or higher is considered obese - a BMI below 18.5 is considered underweight, and between 18.5 to 24.9 a healthy weight. In 2008, 35% of adults aged 20+ were overweight (BMI \geq 25 kg/m²) (34% men and 35% of women) (Figure 6). The worldwide prevalence of obesity has nearly doubled between 1980 and 2008. In 2008, 10% of men and 14% of women in the world were obese (BMI \geq 30 kg/m²), compared with 5% for men and 8% for women in 1980. An estimated 205 million men and 297 million women over the age of 20 were obese – a total of more than half a billion adults worldwide.

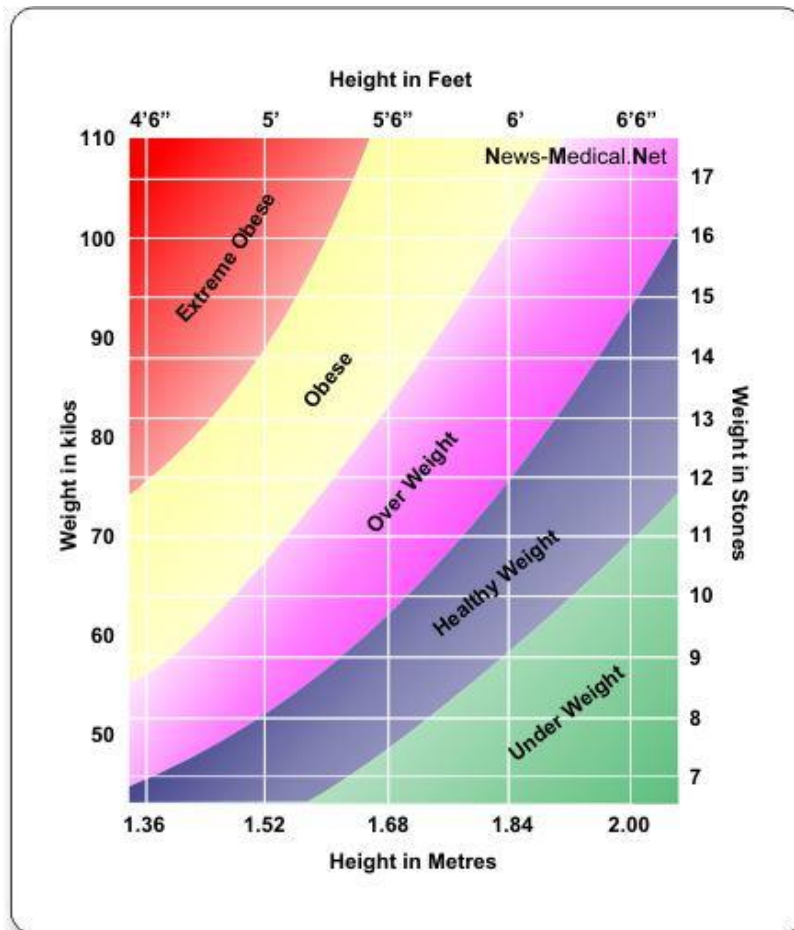


Figure 6: Various Stages of Weight and Obesity With Respect to Height.
(CDC, fact sheets, 2012)

The prevalence of overweight and obesity were highest in the WHO Regions of the Americas (62% for overweight in both sexes, and 26% for obesity) and lowest in the WHO Region for South East Asia (14% overweight in both sexes and 3% for obesity). In the WHO Region for Europe and the WHO Region for the Eastern Mediterranean and the WHO Region for the Americas over 50% of women were

overweight. For all three of these regions, roughly half of overweight women are obese (23% in Europe, 24% in the Eastern Mediterranean, 29% in the Americas). In all WHO regions women were more likely to be obese than men. In the WHO regions for Africa, Eastern Mediterranean and South East Asia, women had roughly double the obesity prevalence of men (27).

Comorbidities

Overweight and obesity lead to adverse metabolic effects on blood pressure, cholesterol, triglycerides and insulin resistance (WHO, GHO, web). Obesity contributes to numerous and varied comorbid conditions. Complications can occur in many organ systems, ranging from cardiovascular to respiratory to orthopedic and even ophthalmologic. Overweight and obesity are known risk factors for heart disease, diabetes, hypertension, gallbladder disease, osteoarthritis, sleep apnea and other breathing problems, and some cancers (uterine, breast, colorectal, kidney, and gallbladder) (28). In addition, obesity is associated with pregnancy complications, high blood cholesterol, menstrual irregularities, hirsutism (excessive hair growth), stress incontinence, psychological disorders, and increased surgical risk (29). Social discrimination against obese persons has a strong negative effect on their quality of life although it was viewed before as a symbol of wealth and fertility, nowadays it is stigmatized by people, and was considered a disease by the World Health Organization in 2013.

Since obesity leads to increased systemic inflammation and it has already been established that DM is associated with increased inflammation, both of these chronic conditions are interlinked and it is thought that increased obesity contributes to excessive systemic inflammation and thus DM.

Periodontal Disease

Periodontology originated from the Greek, they used to call it peri-odous-logos which means around the tooth discourse so the word periodontal literally means around the tooth and it consists of gingiva, cementum, periodontal ligament and alveolar bone (Figure 7). The periodontium starts from the col, which is the tip of the facial interdental papilla and it goes all the way to the trabecular bone which is the cancellous bone (30). Therefore, the common name periodontal disease is a misnomer because the periodontium consists of many structures so there is no one periodontal disease instead it is several clinical conditions affecting different structures and thus we use the term periodontal diseases.

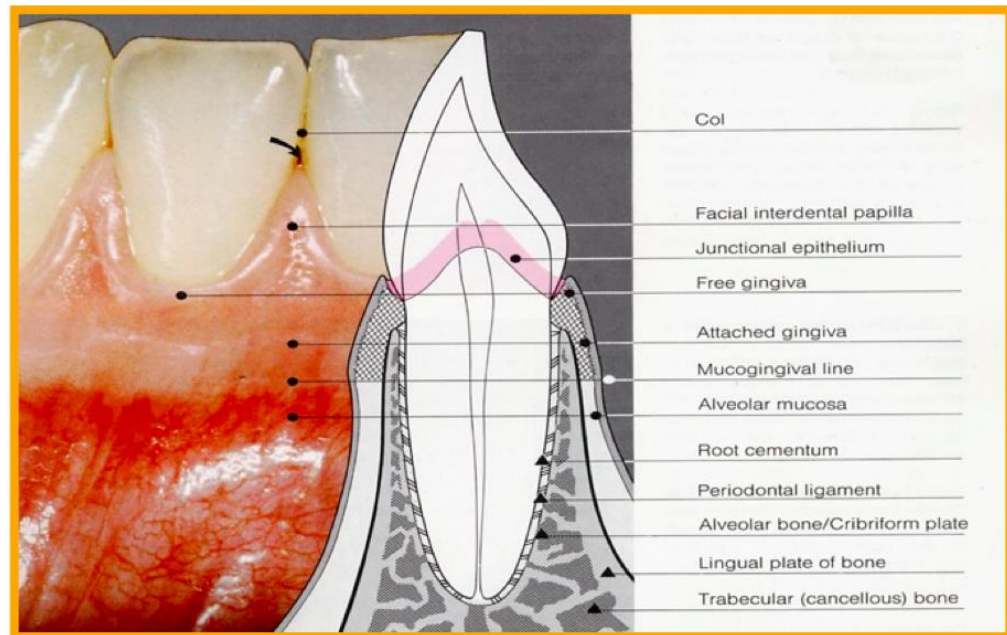


Figure 7: Structure of the Periodontium, The periodontium: schematic drawing of the periodontium with all of its different components. The periodontium: schematic drawing of the periodontium with all of its different components. Figure taken from <http://mouafaqbtc.com/articles/diseases-of-periodontal-ligament/>

Periodontal disease is an infection caused by microorganisms that colonize tooth surface at or below the gingival margin. It is estimated that there are over 700 species that are capable of colonizing the periodontium or the oral cavity in general and the average individual may typically harbor 150 or more different species (31). The microbial organisms that cause periodontal diseases reside in biofilms that subsist on the tooth surface or the surrounding epithelial surfaces. The biofilms are defined as matrix enclosed bacterial populations that are adherent to each other and to other surfaces. Our manifestation of infectious diseases comes from the common

infections people get like skin and upper respiratory infections and those usually show symptoms immediately at the site of infection or elsewhere. The tissues begin to shed if it's a skin infection and if it's an infection of the mucous membranes a constant battle between the organism and the host occurs and the body's immune system usually overcomes the infection in favor of the host. Other systemic infections do not necessarily show symptoms but they are there, like for example those of *Mycobacterium tuberculosis*. This organism colonizes 5% of Americans but only 2.6 per 100 000 new born individuals are reported each year (32). Those 5% of the population are carrying the organism but not showing any symptom of the disease. In a similar fashion, an individual can be colonized by periodontal pathogens at any given time but might not show signs of any of the periodontal diseases and on the contrary to the common diseases that were described above, the unique feature about periodontal disease is that the tooth is a mineralized tissue so no shedding occurs or immediate signs that can be manifested. Instead the pathological process of periodontal diseases is a complex series of events (Figure 8)(33). First the organism must successfully colonize the periodontium, this happens by using adhesins on their surfaces such as fimbriae resulting in adherence to the periodontium structures or other organisms there. They also have to resist being displaced by the flow of saliva, speech and the mouth movement during mastication. After adhering successfully to these structures, they coaggregat and multiply and develop characteristics that evade the host's immune responses. As those pathogens grow and develop they produce toxins that destroy the host's

tissues or cause an inflammatory reaction in the oral cavity that causes destruction of the periodontium. Those virulence factors include enzymes like collagenases, substances that damage tissue cells like hydrogen sulfide and substances that cause cells to produce biologically active substances like lipopolysaccharides (34). So if a mild periodontal disease like gingivitis persists and propagates into deeper tissues of the periodontium, this will lead to deeper tissue destruction, loss of gingival attachment, pathologic alteration of cementum and periodontal ligament and destruction of alveolar bone, this condition is known as periodontitis.

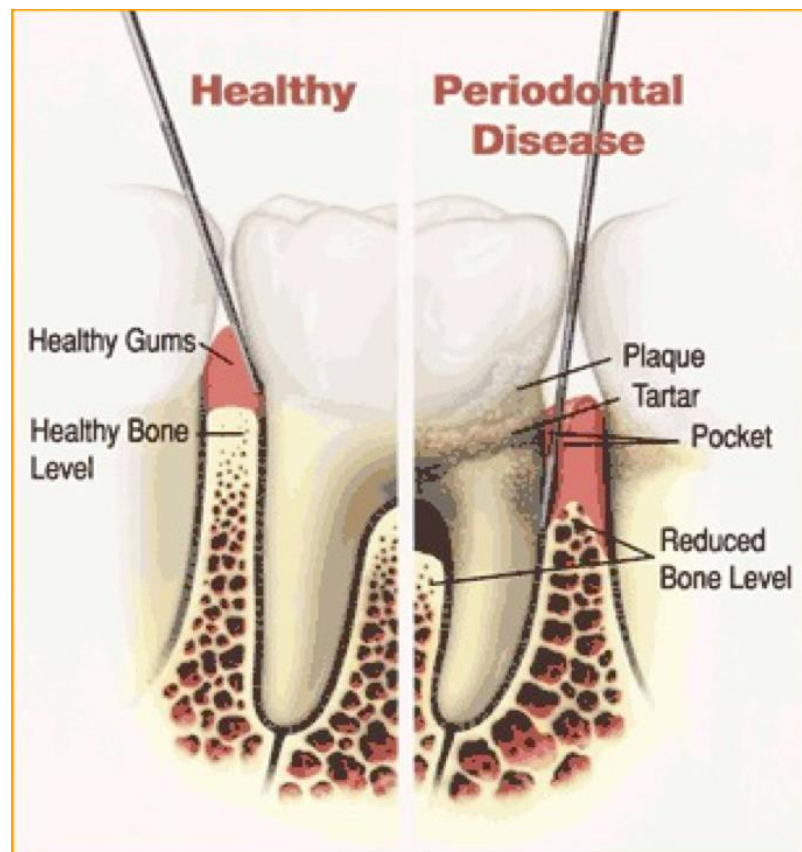


Figure 8: Healthy and Diseased Periodontium. Shown are both the appearance of health gum as well as the build-up of plaque, tartar and increase pocket depth in diseased gum. Figure taken from <http://naturesmile.com/about.php>

In contrast to obesity and diabetes it is difficult to epidemiologically interpret the prevalence of periodontal disease worldwide due to inconsistencies in the methodology used for evaluation (35). However, the American Dental Association (ADA) stated in a recent survey that roughly half of American adults aged 30 or older have some form of periodontal disease, according to Centers for Disease Control and Prevention (CDC) survey data reported Aug. 30, 2012 (36, ADA, 2012). An estimated 47.2 percent, or 64.7 million American, have mild, moderate or severe periodontitis, or gum disease, according to an analysis of data collected as part of CDC's 2009-2010 National Health and Nutrition Survey. Prevalence rates increase to 70.1 percent for adults 65 and older. The data also indicate certain prevalence disparities with respect to race and gender. Periodontal disease is higher in men than women, 56.4 and 38.4 percent respectively and highest in Mexican-Americans, 66.7 percent, compared to other races. The prevalence rate is 64.2 percent for current smokers, 65.4 percent for adults living below the federal poverty level and 66.9 percent for adults with less than a high school education. (37, Center for Disease Control and Prevention (CDC), 2012).

Periodontal disease is diagnosed by probing the gums; a pocket depth greater than 5 mm with bleeding on probing indicate that there is disease (Figure 9).



Figure 9: Probing Depth is a Method for Diagnoses of Periodontal Disease. Shows a periodontal probe being used to determine the pocket depth of a patient. Patient is bleeding on probing which is a sign of periodontal disease, Figure taken from <http://www.spadental.co.uk/blog/2013/08/all-about-gum-disease/>

Periodontal disease is treated by scaling and root planning, or by periodontal surgery if it was more advanced. It is also treated by eliminating the causes of it, for example if the patient smokes, the patient should be encouraged to quit and can be sent to rehab facilities for help. Moreover, for patients taking certain drugs that may affect the periodontal health such as the calcium channel blocker nifedipine for cardiovascular problems, their primary care provider should be contacted and be asked for the possibility of switching to another alternative(38).

Diabetes and Obesity:

One of the most important factors that contribute to diabetes is obesity. It has been known that increased adiposity leads to Type II diabetes for over a century; additionally, epidemiological studies demonstrated a parallel increase in both obesity and Type II diabetes indicating the positive correlation between the two (39). Systemic body conditions associated with an increased body weight and specifically adiposity are well known by now due the enormous amount of studies that were done on that topic (40). It has been estimated that obese people have more than a ten-fold increased risk of developing Type II diabetes compared with normal weight individuals and one study has put increased risk for women with a BMI of 35 or greater at 93 fold. (41). During the last 15 years research has focused on unraveling the underlying biochemical mechanism linking adiposity with Type II diabetes which will be discussed and presented in the results. Ever since the 1950s the term metabolic syndrome became more and more common, Dr. Jean Vague first observed it in 1947 who concluded that upper body obesity predisposes individuals to diabetes, atherosclerosis and gout. Metabolic syndrome is a disorder of energy storage and utilization that is diagnosed when three or more of the following medical conditions co-occur in an individual; abdominal obesity, high blood pressure, high fasting plasma glucose, elevated serum triglycerides, and low high-density cholesterol (HDL) levels. Metabolic syndrome is also called insulin resistance syndrome, this is mainly because in people with large fat deposits, they

have increased amounts of free fatty acids (FFA) in their circulation and this is the main factor that causes insulin resistance. FFA cause insulin resistance by inhibiting insulin mediated glucose uptake into the tissues and so this increases the serum plasma glucose levels. High plasma glucose levels will increase insulin production from the pancreas and so the individual will have hyperinsulinemia. In the liver, FFA increase the production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). The consequence is the reduction in glucose transformation to glycogen and increased lipid accumulation in triglyceride (TG). Insulin is an important antilipolytic hormone. In the case of insulin resistance, the increased amount of lipolysis of stored triacylglycerol molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis.

Figure 10 shows the effect of insulin on various body organs. Insulin decreases overall glucose output in the liver and also increases lipogenesis. In skeletal muscle, it increases the formation of glycogen and increases glucose uptake. In adipocytes, it decreases lipolysis and increases lipogenesis. So the overall effect of insulin is to promote glucose uptake and lipogenesis, also to prevent lipolysis. Insulin resistance causes accumulation of glucose in blood and enhances the production of more insulin from the pancreas, but because of the increased FFA, resistin and cytokines like Tumor Necrosis Factor alpha and interleukin 1, insulin signaling pathway is disrupted and insulin resistance develops. The exact

pathophysiology of insulin resistance is still not known unfortunately but there have been many studies in the literature that investigated the correlation between DM and obesity and almost all of them showed that there is an association between the two clinical conditions. Research done by National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) on Pima Indians who are genetically predisposed to obesity and Type II DM, showed that obesity is a major risk factor for the development of diabetes (42). There are two genetically identical Pima populations, one settled in southern Arizona and the other in a relatively remote region of Mexico. The study found that as a group, the U.S. Pima Indians had more sedentary lifestyles and easier access to higher-calorie processed foods than the Mexican Pima Indians, who exhibited higher activity levels and consumed lower-fat, traditional foods. For this latter population, obesity was uncommon and the prevalence of T2DM was comparable to the U.S. population as a whole. However, strikingly, nearly half of the U.S. Pima population was found to have T2DM and of these, approximately 95% were obese (43). These findings support the idea that people who are more obese and follow an unhealthy sedentary life style are more prone to developing Type II DM.

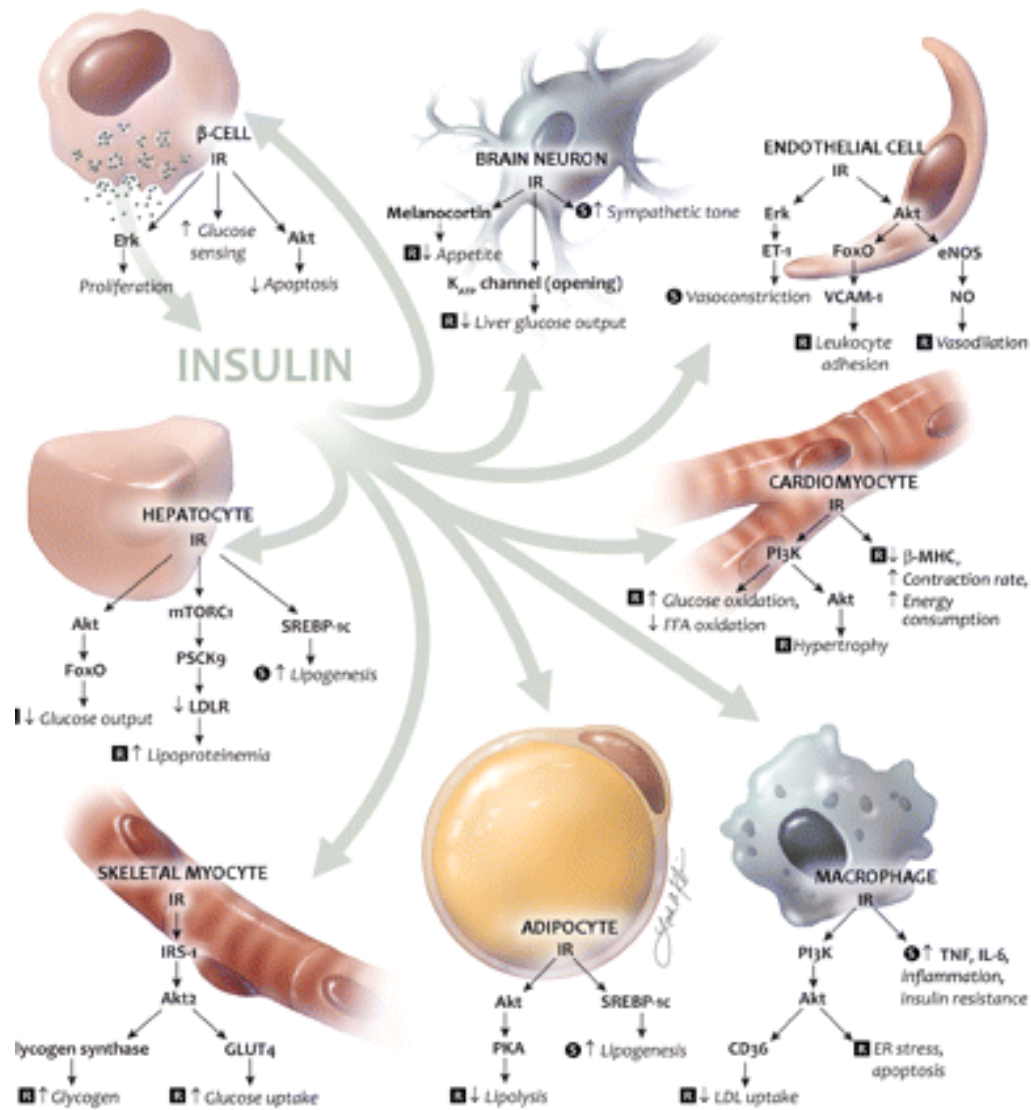


Figure 10: The Effect of Insulin Throughout the Body . Figure taken from Introduction to Insulin Activities from <http://themedicalbiochemistrypage.org/insulin.php>.

Oral Health and Obesity:

Moreover, science and culture completely changed the way they view obesity. Chronic food shortage and malnutrition have been the scourge of humankind from the dawn of history. The current worldwide epidemic of obesity is only few decades old, that was probably defined as such only in the second half of the 19th century(44). The scarcity of food throughout history has led to the connotation that being fat is favorable, it was a sign of wealth, abundance and good health as defined in many books of literature, art and that was the medical opinion at that time. Advances of technology of the eighteenth century have solved this problem and nowadays people have an overabundance of food, technology not only solved the scarcity of food issue but also completely changed people's lifestyles. Jobs that required physical activity no longer exist as everything became computerized or new machinery developed to replace such jobs, people's lifestyles became more sedentary which led to them gaining weight and increased their BMI. People at the time did not know the consequences of such weight gain. Only in the latter half of the 19th century obesity was stigmatized for aesthetic reasons and in the 20th century its association with increased mortality was recognized. What has made this gradual medicalization of obesity alarming is the exponential increase in its incidence over the past 60 years, which led the WHO to declare it a global epidemic and worldwide public-health crisis(45). Over the past decades obesity was associated with heart disease, diabetes, hypertension and many other chronic

diseases as mentioned above in the obesity subsection. Recently, it is being linked to dental health as well, mainly periodontitis. However, studies examining the association between obesity and oral health yielded conflicting results, some showed an association between the two clinical conditions and for others the statistical correlation of such findings were limited to a certain age group; younger adults or even were not significant. When tooth loss was examined and its relationship with obesity, the results were more uniform. It can be concluded that as the number of missing teeth increases, the body mass index (BMI) increases. Fewer studies were done on the relationship between obesity and dental caries and the overall dental health in general. Again conflicting results were gained, obesity could not be a predictor of whether the person would have caries but in general poorer dental health was associated with people with higher BMIs. The relationship between obesity and oral health is bidirectional, bad oral health and more missing teeth affect the quality of food a person can eat, and usually nutrient rich food is replaced with softer, carbohydrate dense type of food which worsens the oral health of an individual even more. Also, people who are obese, usually have an imbalanced diet that is rich in sugar and saturated fat which offers a favorable environment for cariogenic bacteria to thrive in the oral cavity, such as *lactobacilli and mutans streptococci*, which eventually leads to the development of carious lesions. Moreover, obesity has been also linked to suppressed immune response and lead to the development of infectious diseases like periodontitis (46).

Obesity influences unspecific and specific immune responses mediated by humoral and cell mediated mechanisms (47). Unfortunately, the exact molecular and cellular mechanisms linking adiposity and immunity are still not known in details, however evidence from clinical and epidemiological data support the hypothesis that incidence and severity of several infectious diseases are higher in people who are obese than those who are lean, this has been manifested as a poor antibody response to antigens in people whose BMIs are higher than 30. Moreover, findings from Gottschlich and coworkers showed that the incidence and severity of infectious diseases amongst burn patients were higher in obese individuals than lean ones. Thus the ratio of patients who developed bacteraemia and sepsis was more in obese patients (9 out of 15), versus (2 out of 15) in the lean controls (Figure 11). The antibiotic therapy was required for twice as many days for the obese patients than the lean controls but those results were not statistically significant.

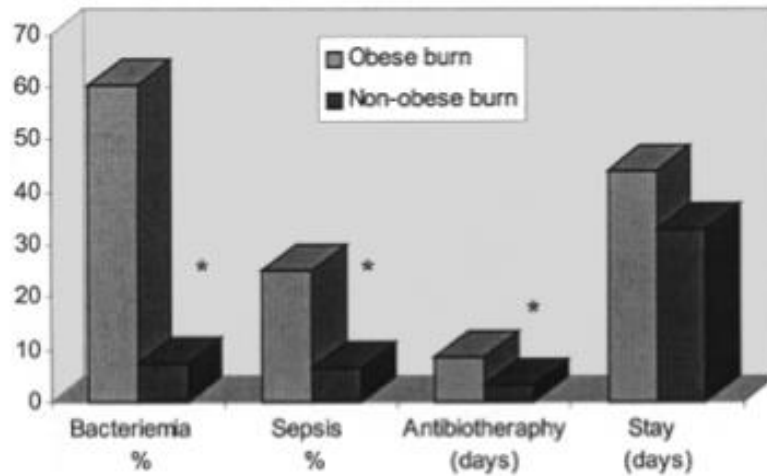


Figure 11: The Effect of Complications and Recovery time in Obese and Non-Obese Patients. Difference between obese and non-obese burn patients at developing sepsis and other bacterial infections . Figure shows that obese patients are at higher risk of developing infections and tend to stay longer in hospitals than their non-obese counterparts. Figure taken from NIH Public Access. Medical and Financial Risks Associated with Surgery in the Elderly Obese. April 2011.

SPECIFIC AIMS

It is known that diabetes has an effect on the condition of the periodontium and often contributes to the progression of periodontal disease. Also periodontal disease leads to worsened glycemic control by increasing the inflammatory status of the body and thus leads to uncontrolled diabetes. Obesity is another global health problem which is associated with several systemic comorbidities as well, such as diabetes, cardiovascular disease, cancer, gall stones...etc (48). As a result excessive obesity leads to diabetes which has been shown to be correlated to periodontal disease. In this study we aim to provide evidence for an underlying mechanism linking diabetes, obesity and periodontal disease by studying the relationship and interactions of these three systemic conditions and eventually gain an understanding of what is currently called a triangular relationship.

In addition to this, we aim to highlight to dental practitioners the importance of prevention and treatment of periodontal disease and the role they play in helping to reduce the burden of related systemic diseases. We hope that this study will clarify the relationship between diabetes and obesity with respect to periodontal disease.

PUBLISHED STUDIES

Adipose tissue is no longer considered as merely a depository of fat containing cells; it is now seen as an active endocrine organ with adipocytes, like many other cells, capable of releasing hormones, the best known being leptin, the appetite controlling hormone and cytokines. These small proteins with a typical molecular weight in the range 8,000– 40,000 (49), which are related not by structure but by their common cellular signaling action, including the regulatory mechanism that determines the body's reaction to cellular trauma and infection by either promoting or suppressing the inflammatory response (50). The cytokines secreted from the adipocytes are called adipokines and are secreted into the blood circulation where they mediate an inflammatory activity in the body system. The adipokines that show a proinflammatory action are Tumor Necrosis Factor alpha (TNF- α) and Interleukin (IL)-6 (IL-6) (51). Excessive secretion of adipokines is linked to the pathogenesis of diabetes. Thus excessive obesity can cause systemic inflammation and can mediate diabetes. This is because the increased circulating inflammatory chemokines, cytokines and adipokines disrupt insulin signaling in tissues like the liver and skeletal muscle and lead to insulin resistance and the onset of diabetes mellitus. While this evidence does not establish a causal relationship, the epidemiological data showing a parallel rise in obesity and Type 2 diabetes prevalence, both accompanied by raised levels of circulating pro-inflammatory cytokines, reinforces the belief in an inflammatory mediated metabolic mechanism

(52). The mechanism that is generally accepted to show causality is that a high calorie diet leads to accumulation of fatty acids in adipose tissue induces adipocyte hypertrophy and increases the production of reactive oxygen species (ROS) leading to the activation of adipose tissue inflammation and increased expression of cytokines (53). Upregulation of cytokines stimulates the infiltration of chronic inflammatory cells such as macrophages. These cells further accelerate inflammation by secreting more pro-inflammatory cytokines and chemoattractants (chemokines) causing further infiltration of chronic inflammatory cells and a further rise in pro-inflammatory adipokine secretion, thus initiating a self-generating reciprocal cycle of chronic inflammation (54). Increased levels of circulating free fatty acids, reactive oxygen species and inflammatory cytokines disrupt insulin signaling in organs such as skeletal muscle and the liver, leading to β cell dysfunction, systemic insulin resistance and the onset of diabetes mellitus (55). This was known because adipokines and adiposity were mirrored in the increase, circulating adipokines were found in higher concentrations in people with Type II diabetes (56).

Chronic Inflammatory Periodontal Diseases

Chronic inflammatory periodontal diseases are the most common inflammatory conditions among humans; periodontitis affects approximately 50% of adult population. (57) In persons with periodontitis the inflammatory response is responsible for destroying host tissue, which leads to inflammation of the gums,

recession and eventually tooth loss. There is increasing evidence that it also leads to systemic inflammation by either direct access of the pathological bacteria in the mouth to the blood circulation through bleeding during brushing or flossing (58), or the bacteria in the plaque biofilm actually invade the endothelial tissue and access the systemic circulation thus leading to an inflammatory response or exacerbating an already present inflammation, which in turn leads to poor diabetes control and worsened diabetes complications. A recent study from China examined the ability of *porphyromonas gingivalis* to invade human umbilical vein endothelial cells (HUVECs) and to study its effect on the production of nitric oxide (NO) and on the expression of inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS). The study completed using electron microscopy showed that *P. gingivalis* ATCC 33277 can adhere to HUVECs by fimbriae, invade the HUVECs and exist in the cytoplasm and vacuoles (59). The interaction between *P.gingivalis* and HUVECs showed that *P. gingivalis* were adhering to the HUVECs via fimbriae, and the HUVECs had microvilli protruding from their surfaces and interacting with the fimbriae. *P. gingivalis* ATCC 33277 was localized in the cytoplasm of HUVECs after co-incubation for 8 h. *P. gingivalis* ATCC 33277 was also detected within vacuoles in HUVECs (ref). (Figure 12) Periodontal disease and Type 2 diabetes have a two-way relationship (60). People with Type 2 diabetes have an increased prevalence and severity of periodontal disease (61).

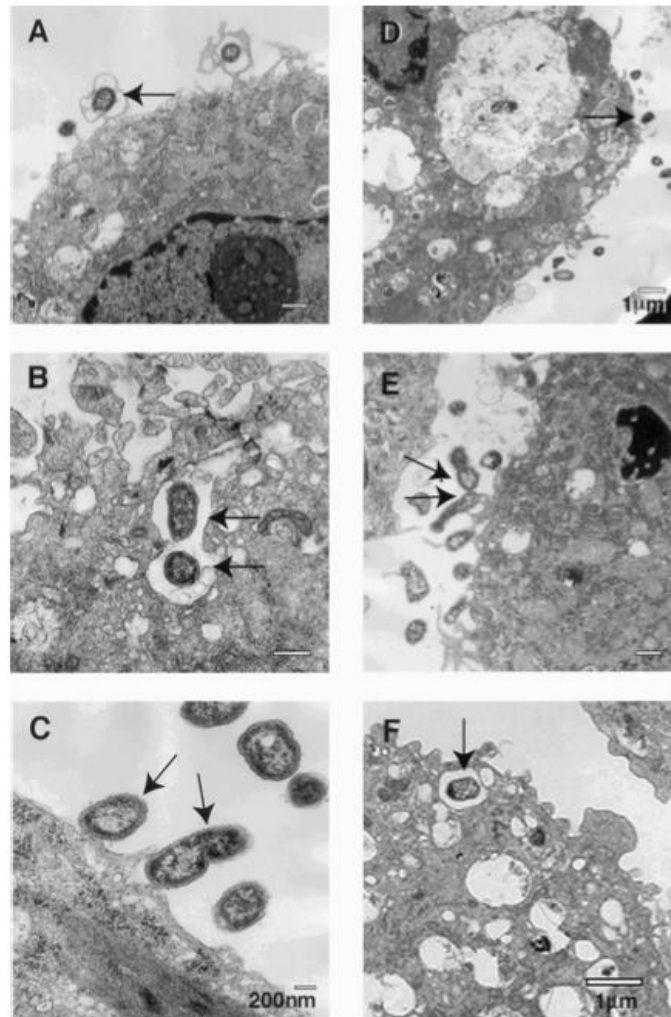


Figure 12: *P. gingivalis* Adheres to HUVECs via Fimbriae . Transmission electron micrographs demonstrating *P. gingivalis* invasion of EC. (A and B) BAEC with *P. gingivalis* A7436. (A) At the cell surface, bacteria appear to induce EC structural rearrangements consistent with an endocytic mechanism. (B) Internalized bacteria are found within vacuole. (C) BAEC with *P. gingivalis* 381. Note the apparent contact between microfilamentous cellular components and surface-adhering *P. gingivalis*. (D) BAEC with *P. gingivalis* *fimA* mutant DPG3. Absence of intimate interaction between EC surface and bacteria. (E and F) FBHEC incubated with *P. gingivalis* A7436. Surface adherence (E) and engulfment in vacuole (F). Arrows in all panels point to *P. gingivalis*. Bars on each image are 0.5 μm unless otherwise specified. Composite image was constructed with Adobe Photoshop 3.0. Original figure taken from (infection and Immunity Journal, 1988, 64).

There is also evidence that periodontal disease can exacerbate worsening glycemic control in patients with Type 2 diabetes. Inflammation is key to this two way relationship. Type 2 diabetes is preceded by systemic inflammation which leads to reducing the function of pancreatic beta-cells, their apoptosis and eventually the development of insulin resistance. Recent studies have showed that increased systemic inflammation (acute-phase and oxidative stress biomarkers) results from the entry of periodontal pathogens and their virulence factors into the circulation, providing biological plausibility for the effects of periodontitis on diabetes (62). AGE (Advanced Glycation End products)– RAGE (Receptor for AGEs) interactions and oxidative-stress-mediated pathways provide plausible mechanistic links in the diabetes to periodontitis direction (63). It is thought that the periodontal pathogens can invade endothelial cells using the fimbriae and fimbriin like peptides, which associate with Toll like receptors 2 that are the most prominent type of receptors on the endothelial cells.(64) A recent study done by *Boston University School of Medicine*, studied this; they utilized 41 kDa (major) and 67 kDa (minor) fimbria mutants to demonstrate that major fimbria are required for efficient *P. gingivalis* invasion of human aortic endothelial cells (HAEC). The researchers used enzyme-linked immunosorbent assay (ELISA) to detect the presence of the proteins; ELISA test showed that only invasive *P. gingivalis* caused HAEC production of pro-inflammatory molecules interleukin (IL)-1 β , IL-8, monocyte chemoattractant

protein (MCP)-1, intracellular adhesion molecule (ICAM)-1, vascular cellular adhesion molecule (VCAM)-1 and E-selectin. The purified native forms of major and minor fimbria induced chemokine and adhesion molecule expression similar to invasive *P. gingivalis*, but failed to elicit IL-1 β production. In addition, the major and minor fimbria-mediated production of MCP-1 and IL-8 was inhibited in a dose-dependent manner by *P. gingivalis* lipopolysaccharide (LPS). Both *P. gingivalis* LPS and heat-killed organisms failed to stimulate HAEC. Treatment of endothelial cells with cytochalasin D abolished the observed pro-inflammatory MCP-1 and IL-8 response to invasive *P. gingivalis* and both purified fimbria, but did not affect *P. gingivalis* induction of IL-1 β .

Obesity

Recent evidence has begun to emerge that obesity might have a greater role in this inflammation than was previously thought. Since obesity leads to systemic inflammation, it can impact the oral cavity, particularly the periodontium. The first report on the relationship between obesity and periodontal disease appeared in 1977, when Perlstein *et al.* found alveolar bone resorption to be greater in obese rats compared with non-obese rats (65). This correlation was supported by further evidence from studies that established a relationship between increased body mass index and deepened periodontal pockets (66). Recent evidence links the hip to waist ratio and periodontitis. Recent studies have found that central fat (belly fat) was associated with worse periodontitis conditions (67). Although most evidence has

come from cross-sectional data, strong evidence has come recently from three longitudinal studies in the USA, one showing significant periodontal disease progression over 25 years in obese men (68) and the second, a very large study of 36,910 health care professionals showed a significant association, even among the non-diabetic and never-smoking over a period of up to 20 years.(69) In a third study a five-year follow-up of 3,590 Japanese subjects showed evidence of a dose-response association between BMI and periodontal disease (70) . The metabolic pathway of a causal relationship between obesity and periodontitis remains to be confirmed, but it is possible that increased secretion of inflammatory mediators may modify the response of the periodontal tissues to the oral environment and the production of excessive amounts adipokines from the adipose tissue could produce this effect (71) . There is evidence linking periodontal disease with metabolic disorder, an increasingly common loose association of abdominal obesity, abnormal fat metabolism, hypertension, insulin resistance, high plasma fibrinogen and elevated CRP (72) . Another study whose aim was to examine whether overweight and obesity indicators like body mass index (BMI), waist circumference (WC), and WC-to-height ratio, predict progression of periodontal disease in men showed that Body mass index and WC-to-height ratio were significantly associated with hazards of experiencing periodontal disease progression events regardless of periodontal disease indicator. Adjusted hazard ratios for periodontal disease progression were 41–72% higher in obese men (BMI 30 kg/m²) relative to men with both normal weight and WC-to-height ratio (50%) (73) . This proves that periodontal disease

and certain obesity related systemic illnesses are related through an inflammatory mechanism, with abnormal fat metabolism possibly being an important factor. (74)

DISCUSSION

This paper researched the correlation between three very popular chronic diseases, periodontal disease, diabetes and obesity. All three of them are trending nowadays and more and more people are being affected by them. What is in common among all three of them is the impact it has on the individual, obesity restricts someone's movement, causes joint and muscle pain and is also the cause of so many other clinical conditions. It has been established that obese people; people with BMI 30 or higher are at increased risk of hypercholesterolemia, high blood pressure, gallstones, osteoarthritis and among them is diabetes (75). This is because adipose tissue is not just a mere deposit of fats but it is an active endocrine gland that releases hormones and inflammatory cytokines into the blood circulation; these cytokines are called adipokines and they exacerbate an already present inflammatory response in the body. Diabetes is preceded by a phase of increased inflammation which leads to the destruction of the islet cells of Langerhan in the pancreas and thus leads to a decreased insulin production. Also increased obesity contributes to the development of diabetes through metabolic syndrome which leads to insulin resistance. This occurs because of the increased circulating FFA released from the adipose tissue, which prevent the insulin activated glucose uptake into the tissues and thus leads to hyperglycemia of the blood and the further release of more insulin and thus the condition of insulin resistance that leads to diabetes if left untreated for a prolonged time. Diabetes in turn has its

manifestations on the body, diabetics are more prone to skin infections, eye infections and other complications because it leads to the development of cataracts and glaucoma, neuropathy and poor wound healing (76). Among its manifestations is periodontitis, people with diabetes are at increased risk for developing periodontitis, this is partly because diabetics have xerostomia a condition also known as dry mouth, that leads to a decreased salivary flow and thus the oral cavity will be more prone to ulcers and infections like tooth cavities and periodontitis. In addition to this, diabetes leads to thickening of blood vessels so the tissues in the oral cavity will not get the necessary nutrients and blood flow so they will be more prone to infections. Moreover, recent evidence proved that the relationship between diabetes and periodontitis is a two way relationship, that periodontitis might also lead to the development of type II DM and worsening glycemic control in diabetics (77) . The theory behind this is that the oral pathogens can access the systemic circulation either through bleeding when brushing or flossing or by special mechanisms. These mechanisms include invasion of endothelial cells by fimbriae and fimbriin-like peptides on their surfaces when they adhere to the walls of the endothelial cells they go in via endocytosis and causing an overall systemic inflammation which again leads to the development of diabetes and other chronic diseases like heart disease and atherosclerosis. This is because when pathogens invade endothelial cells they produce a procoagulant effect in the blood and also enhance the deposition of lipids on the arterial walls which leads to the development of atherosclerosis. All in all, this study shows that one can not separate

oral health from systemic health, physicians and primary care practitioners should be more aware of this association and people with uncontrolled diabetes should be referred to a dentist to have their oral condition checked regularly due to the association between the two diseases. Also people who are relatively obese should be warned about their life style by both their dentist and primary care physician and should be advised to change their eating habits, to exercise more often and to lower their weight due to the associated systemic and oral health complications.

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CURRICULUM VITAE

