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A STUDY TO EVALUATE GINGIVAL CREVICULAR BLOOD AS A SCREENING TOOL FOR BLOOD GLUCOSE CONCENTRATION

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ABSTRACT

A study to evaluate gingival crevicular blood as a screening tool for blood glucose concentration

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Introduction

There is a high prevalence of type 2 diabetes mellitus (DM) in the UAE. Recent national guidelines advise screening for undiagnosed diabetes in all adults aged ≥ 30 years. This study assessed the feasibility of identifying undiagnosed diabetes and prediabetes using gingival crevicular blood in patients with periodontitis.

Material and Methods

Twenty healthy controls (Group I) and twenty known diabetics (Group II) were recruited from the Periodontics Department in a cross-sectional study of 40 adults with chronic periodontitis. Gingival crevicular blood and capillary finger blood glucose concentration obtained during routine periodontal examination were analyzed by an Accu–Chek® Performa self-monitoring device. Diurnal effects were controlled.

Results

The mean age for Group I was 39.5 years (9.8) and for Group II it was 45.5 (10.2) with no significant difference by age between the two groups. The mean duration of diabetes in Group II was 5.7 (3.2) years. Mean blood glucose concentration from gingiva and finger within each group were not significantly different. Mean finger blood glucose concentration in Group II was significantly higher at 172(47) mg/dL than for Group I, 115.1(17) mg/dL ($t=5.03$, $p<0.001$). Similarly, mean gingival blood glucose was significantly higher in Group II compared to Group I, 173.2 (47.7) mg/dL and 116.3 (16.7) mg/dL respectively ($p<0.001$). There was a very strong correlation between mean blood glucose from finger capillaries and

gingiva (0.996; $p<0.001$) within each group irrespective of gender, age, periodontitis and duration of diabetes. The duration of diabetes was highly predictive for both gingival and finger blood glucose concentration ($p<0.001$). Within Group I, 5 of the 20 patients were identified as pre-diabetic with a blood glucose concentration above 140 mg/dL.

Conclusions

Gingival crevicular blood glucose can be measured with the Accu-Chek® Performa safely and easily to screen for the diabetic status of patients with bleeding on probing.

DEDICATION

To my Parents,

For raising me to believe that anything was possible

And for my Husband,

For making everything possible.

DECLARATION

I declare that all the content of the thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Asmaa Khaliefah Alhammoudi

Signature:

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ABBREVIATIONS

AAP: American Academy of Periodontology.

ADA: American Diabetes Association.

AGEs: advanced glycosylation end products.

CAL: Clinical attachment loss.

CFB: Capillary finger blood.

CPI: Community Periodontology Index.

EFP: European Federation of Periodontology.

GCB: Gingival crevicular blood.

GCF: Gingival crevicular fluid.

GCP: Good Clinical Practice.

HBA1C: hemoglobin A1c

PD: probing depth.

PMNs: polymorphonuclear neutrophils.

SPSS: Statistical Package for Social Sciences.

T2DM: type II diabetes mellitus.

WHO: World Health Organization.

1. INTRODUCTION

The epidemic of type-two diabetes mellitus (T2DM) is evident globally, shortening lives and straining the financial resources of health care systems. Several statistics indicate that the Gulf region has high risk factors for diabetes. In the UAE, the prevalence of type-two diabetes is the second highest in the world with 19% of the adult population between the age of 20 to 70 years being affected. [(1)]

The ministry of Health in the UAE has brought together local scientists and experts to draw up strategies and national programs to increase public awareness as a first step in controlling the disease.

Strengthening of the collaboration and joint planning between different health authorities in the UAE, through the development of a national planning framework is highly recommended to reduce the burden of the T2DM epidemic and improve the quality of its care.

Dentists are uniquely placed to increase public awareness of T2DM and in the early detection of prediabetes. Because of the close relationship between diabetes and periodontitis, it can be assumed that dental practitioners are extremely likely to encounter many patients having both diabetes mellitus and periodontitis. A high number of patients with periodontitis may have undiagnosed diabetes. The early diagnosis of diabetes might help to prevent or reduce its long-term complications which are responsible for the high morbidity and mortality of diabetic patients. [(2)]

While finger capillary blood glucose measurement is a common screening tool, dental practitioners, may find gingival blood more convenient as a blood sample which can be obtained during routine scaling. The strip system may provide a simple, quick and reliable method to measure glucose concentration and identify prediabetes using gingival blood.

2. LITERATURE REVIEW

2.1. Review of the literature of Diabetes

2.1.1 Definition of diabetes mellitus

Diabetes mellitus is defined as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both.

T2DM was formerly called non-insulin-dependent, or adult-onset which results from the body's ineffective use of insulin. T2DM affects the majority of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. [3]

Symptoms may be similar to those of type 1 diabetes, but are often less marked. As a result, the disease may be diagnosed several years after onset, once complications have already arisen.
Until recently, this type of diabetes was seen only in adults but it is now also occurring with increased frequency in children.

2.1.2 History of diabetes mellitus

For 2,000 years diabetes has been recognized as a devastating and deadly disease. In the first century A.D. a Greek physician, Aretaeus, described the destructive nature of the affliction, which he named "diabetes" from the Greek word for "siphon". Physicians in ancient times, recognized the symptoms of diabetes but were powerless to treat it effectively. In the 17th century a London physician, Dr. Thomas Willis, determined whether his patients had diabetes or not by sampling their urine. If it had a sweet taste he would diagnose them with diabetes mellitus-"honeyed" diabetes. This method of monitoring blood sugars went largely unchanged until the 20th century.

Before the discovery of the insulin little could be done for patients suffering from diabetes. Low calorie diets prolonged their lives but left them weak and near starvation.

Banting and co-workers [(4)] went on to purify the hormone insulin from bovine pancreases at the University of Toronto. This led to the availability of an effective treatment—insulin injections—and the first patient was treated in 1922. The first successful patient treated was a 14-year-old boy who weighed only 65 pounds. When he was given the extract on January 1922, his ketonuria and glycosuria were almost eliminated. His blood sugar levels dropped as low as 77%. Six more patients were treated in February 1922 and quickly experienced an improved quality of life.

A pharmaceutical company in conjunction with the University of Toronto, began the mass production of insulin and by the end of 1923, 25000 patients were being treated in Canada and the United States [(5)]. For this, Banting and laboratory director John Macleod received the Nobel Prize in Physiology or Medicine in 1923. In the ’50s, it was discovered that there were two types of diabetes: "insulin sensitive" (type I) and "insulin insensitive" (type II).

Two thousand years have passed since Aretaeus spoke of diabetes as "the mysterious sickness". It has been a long and arduous process of discovery, as generations of physicians and scientists have added their collective knowledge to finding a cure. It was from this wealth of knowledge that the discovery of insulin emerged in a small laboratory in Canada. Since then, medical innovations have continued to make life easier for people with diabetes.

2.1.3 Diagnostic criteria for diabetes mellitus [6]

The American Diabetes Association (ADA, 2011) gives the following criteria for the diagnosis of diabetes:

- HBA1C ≥ 6.5%. The test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
- Fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.
- 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
- In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
- In the absence of unequivocal hyperglycaemia, the result should be confirmed by repeat testing.

2.1.4 Classification of diabetes mellitus [3]

Until recently, the prevailing conceptual classification were two primary types of diabetes mellitus: autoimmune (type 1) and nonautoimmune (type 2).

Every other metabolic disorder of glucose regulation was classified into a special category of (mostly type 2 related, nonautoimmune) diabetes, such as, monogenic, gestational, steroid induced, cystic fibrosis related, postpancreatectomy, acromegaly associated, human immunodeficiency virus (HIV) associated, hepatitis C virus associated, polycystic ovary syndrome related, and ketosis prone diabetes.

Moreover, Impaired glucose tolerance and impaired fasting glucose can indicate a condition called pre-

diabetes. These individuals are normoglycemic but demonstrate elevated blood glucose levels after fasting and after glucose load. This condition is a strong predictor for future development of T2DM. [7]

2.1.5 Complication of diabetes mellitus

It is well recognized that the pathogenesis of diabetes mellitus induces long-term irreversible damage of various tissues and organs. Chronic hyperglycemia plays a major role in the production of several systemic complications and these considerably reduces life expectancy. These complications can be categorized as macrovascular and microvascular.

Macrovascular complications:

These are responsible for the majority of the morbidity and mortality associated with the disease. Hyperglycemia predisposes to atherosclerosis and vascular obstruction, which is accountable for the increased likelihood of coronary artery disease, cerebrovascular disease and peripheral vascular disease [8] These patients are twice as likely to experience strokes and three to five times more likely to experience myocardial infarctions. [9]

Microvascular complications:

These tend to manifest 10−20 years after diagnosis in young patients, and result from the chronic hypertension associated with macrovascular obstruction [8] They typically include:

- ✓ Retinopathy: Between 80−90% of diabetics develop retinopathy after 30 years [9]. The condition predisposes to earlier development of cataracts and is the most common cause of blindness.
- ✓ Nephropathy: A major cause of premature death in diabetics, manifesting in 25−35% of patients diagnosed [9]. Most damage is a result of glomerular hypertension, ischemia and ascending infection, eventually leading to kidney failure.

- ✓ Neuropathy: Results from disruption of the function of peripheral nerves, delaying nerve conduction and causing axon demyelination. This causes a loss of protective sensation and an increased risk of limb amputation. ‘Burning’ feet are common descriptions from patients. [9]

Although this diagram is comprehensive in showing many clinical manifestation and complications of diabetes mellitus, it fails to indicate the association with periodontal diseases!

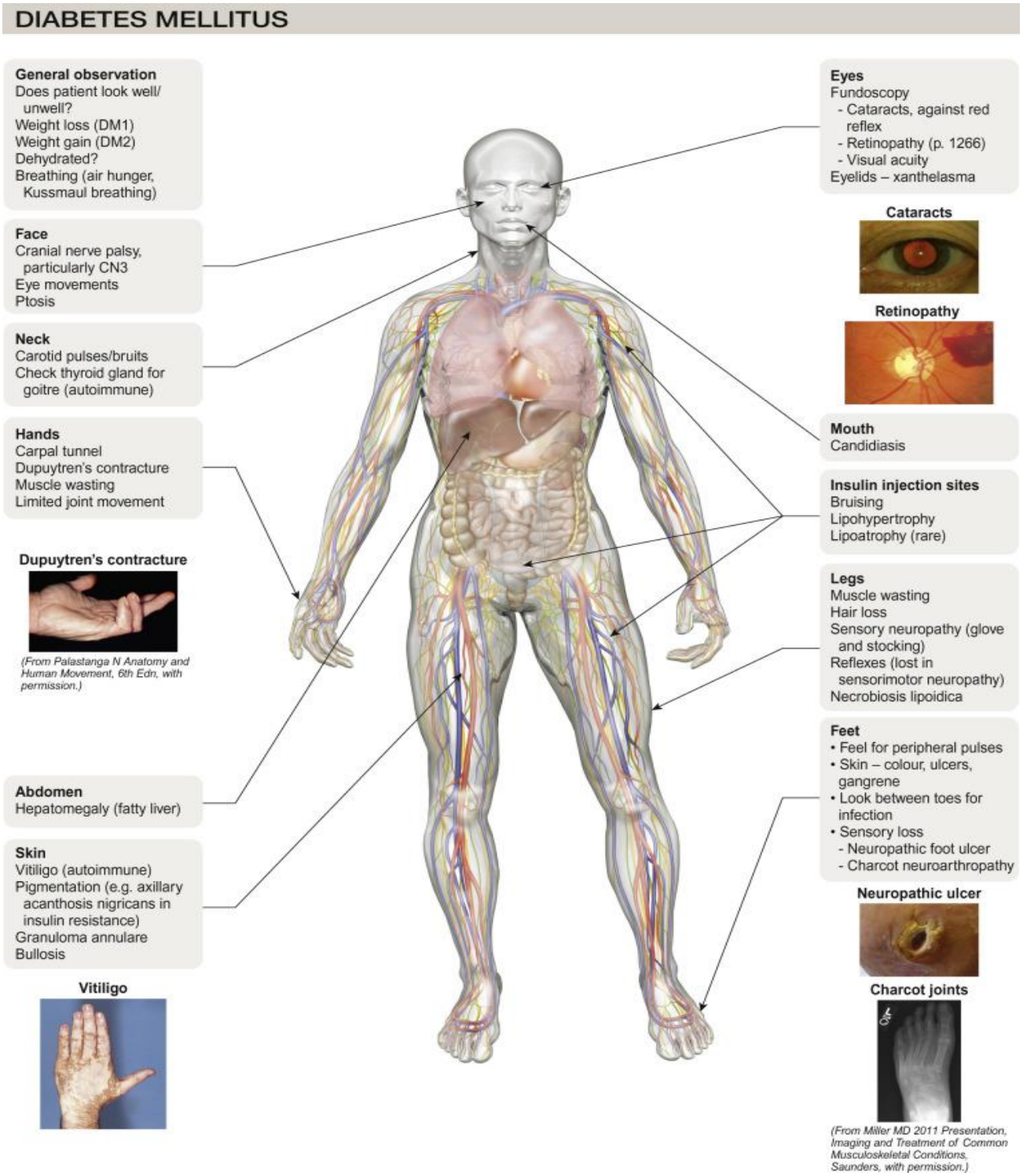


Figure 1: Clinical manifestations and complications of diabetes mellitus. [8]

2.1.6 Oral manifestations of diabetes

There is abundant evidence that diabetes is associated with pathological changes in the oral cavity.

These changes include mucosal ulceration, fungal infection, burning mouth syndrome, tooth loss, xerostomia, dental caries and periodontal disease. [10]

These manifestations are more pronounced among patients with uncontrolled blood glucose levels. [11]

Lacey and Timms [12] found that pathological changes in the oral cavity are one of the early signs of diabetes.

Careful examination of the oral cavity may identify indications of an underlying systemic condition, and allow early diagnosis and treatment. The examination should include an assessment of changes to the mucosa, periodontal inflammation, and bleeding, as well as the general state of the teeth.

As diabetes may remain undiagnosed for a long time, dentists could be instrumental in facilitating early detection of diabetes. Early detection is the key factor for prevention of medical complications, as well as the economic burden related to management of the disease.

Table 1 shows the pathophysiology, treatment, and prevention aspects of orofacial diseases related to diabetes.

Table 1. The pathophysiology, treatment and prevention aspects of orofacial diseases related to diabetes millatus (DM). [13]

Oral pathology related to DM	Pathogenesis	Treatment and Prevention
Periodontal disease	Accumulation of AGEs in periodontal tissues, decreased periodontal regenerative capacity and defective immune regulation	Assessment of risk of disease progression, periodic reviews, dietary advice and periodontal therapy
Dry mouth	Reduced salivary flow as a result of polyuria and dehydration	Proper control diabetes and dental hygiene
Root Caries	As a result of gingival recession and decreased salivary flow	Use of fluoridated pastes, restorative treatments. The optimal glycemic control prevents progression
Oral Candidiasis	Due to salivary dysfunction, hyperglycemia and impaired immune system	Antifungal nystatin or miconazole treatment. Good glycemic control and prevention
Pulp necrosis and periodontal abscess	Ischemic tissue damage	Endodontic treatment and control of diabetes
Delayed wound healing and increased incidence of infections following surgery	Caused by vascular dysfunction and decreased immune on diabetes	Preventive administration of antibiotics and good glycemic control

*AGEs: advanced glycosylation end products.

2.1.7 Diabetes in the United Arab Emirates

The epidemic of T2DM is evident globally, shortening lives and straining the financial resources of health care systems. Especially in the UAE, the prevalence of type-two diabetes is the second highest in the world at 19% of the adult population between the ages of 20 to 70 years [1]. If no action is taken and the current trends continue, by 2020 an estimated 32% of the adult population between ages of 20 to 79, including both UAE nationals and expatriates will become diabetic.

Diabetes treatment constitutes 40 percent of the UAE's overall health care expenditures, at $6.6 billion or 1.8 percent of GDP. [14], [15]

Nikolopoulou and Kangas 2011 [16] developed a System Dynamics model to capture the prevalence of T2DM in the UAE and the impact of the basic variables (Willingness to Advocate, Policy Driven Awareness and Number of Recommended Annual check-ups) on its growth.

Of these variables the one with the highest impact is people's awareness. Given the fact that awareness is mostly driven by policies that could be potentially applied, an effective strategy could be developed directed at an increase in the awareness of people regarding the mechanism and severity of the disease.

Another study carried out by Imperial college London in Abu Dhabi [17] provided a picture overview of T2DM prevalence and risk factors contributing to its adverse outcomes in the UAE. They concluded that strengthening the collaboration and joint planning between different health authorities in the UAE through the development of a national planning framework is highly recommended to reduce the burden of the T2DM epidemic and improve the quality of care.

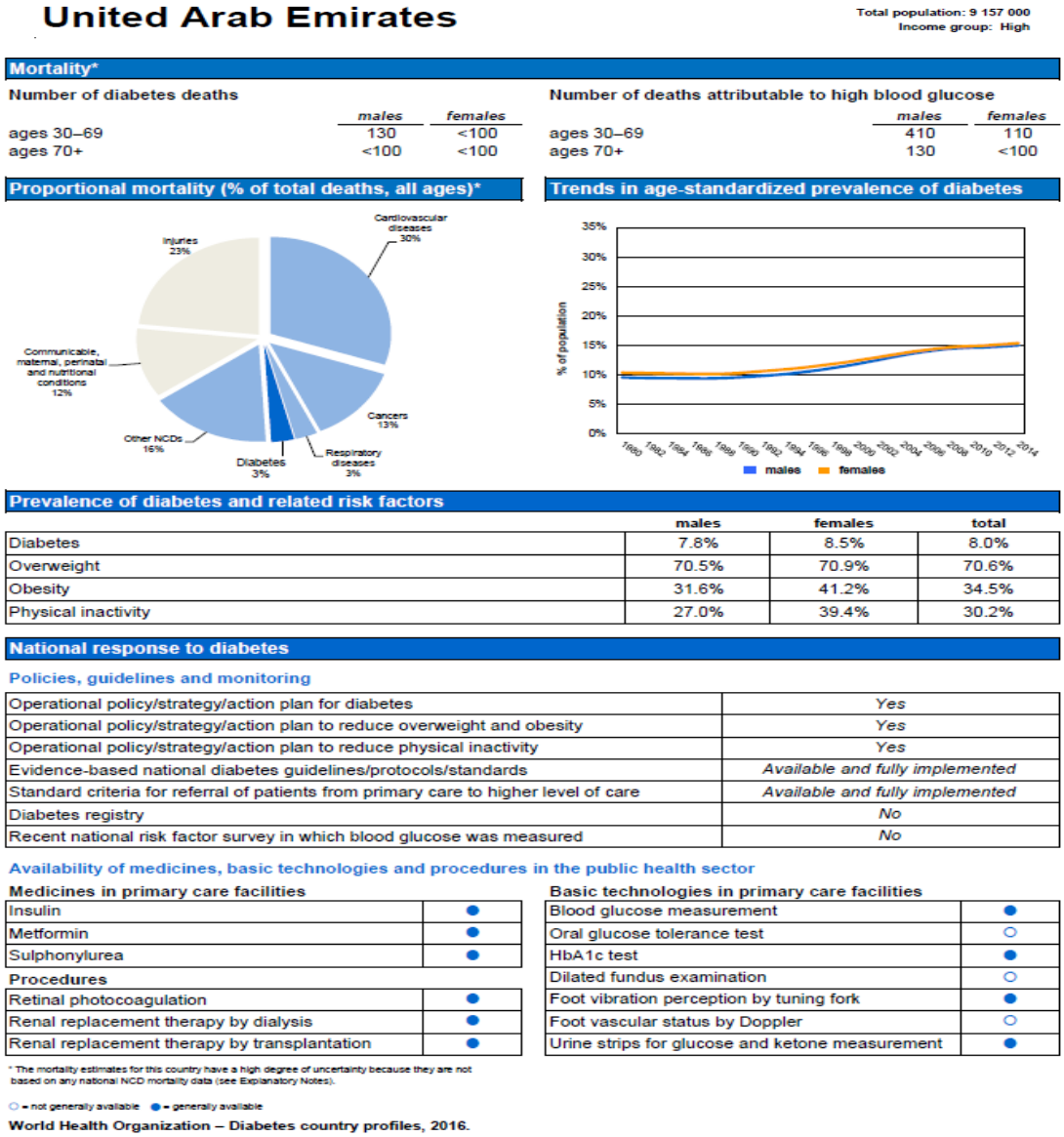
Additionally, reinforcing the role of primary care in providing T2DM care and strengthening the collaboration and co-ordination between the primary and secondary care settings in the UAE is required

to optimize the care provided to people with T2DM [17]. Dental care should be a part of this collaboration and provide a common clinical pathway including dental care for patients with T2DM.

The dental visit provides an important potential venue for diabetes screening. This should be strongly considered when policy makers generate guidelines and Care Pathways.

2.1.8 The UAE diabetes profile.

The aim of the diabetes country profiles is to synthesize, in one reference document, the national status of diabetes prevention and control. The UAE diabetes profile include data on diabetes prevalence and trends; mortality; risk factors; availability of diabetes country plans; monitoring and surveillance; primary prevention and treatment policies and availability of medicines, basic technologies and procedures.



United Arab Emirates

Total population: 9 157 000
Income group: High

Mortality*

Number of diabetes deaths

	males	*females*
ages 30–69	130	<100
ages 70+	<100	<100

Number of deaths attributable to high blood glucose

	males	*females*
ages 30–69	410	110
ages 70+	130	<100

Proportional mortality (% of total deaths, all ages)*

Trends in age-standardized prevalence of diabetes

Prevalence of diabetes and related risk factors

	males	females	total
Diabetes	7.8%	8.5%	8.0%
Overweight	70.5%	70.9%	70.6%
Obesity	31.6%	41.2%	34.5%
Physical inactivity	27.0%	39.4%	30.2%

National response to diabetes

Policies, guidelines and monitoring

Operational policy/strategy/action plan for diabetes	*Yes*
Operational policy/strategy/action plan to reduce overweight and obesity	*Yes*
Operational policy/strategy/action plan to reduce physical inactivity	*Yes*
Evidence-based national diabetes guidelines/protocols/standards	*Available and fully implemented*
Standard criteria for referral of patients from primary care to higher level of care	*Available and fully implemented*
Diabetes registry	*No*
Recent national risk factor survey in which blood glucose was measured	*No*

Availability of medicines, basic technologies and procedures in the public health sector

Medicines in primary care facilities

Insulin	●
Metformin	●
Sulphonylurea	●

Procedures

Retinal photocoagulation	●
Renal replacement therapy by dialysis	●
Renal replacement therapy by transplantation	●

Basic technologies in primary care facilities

Blood glucose measurement	●
Oral glucose tolerance test	○
HbA1c test	●
Dilated fundus examination	○
Foot vibration perception by tuning fork	●
Foot vascular status by Doppler	○
Urine strips for glucose and ketone measurement	●

* The mortality estimates for this country have a high degree of uncertainty because they are not based on any national NCD mortality data (see Explanatory Notes).

○ = not generally available ● = generally available

World Health Organization – Diabetes country profiles, 2016.

Figure 2: The UAE Diabetes profile by (2016 by WHO).

2.2. Review of the literature of periodontal diseases

2.2.1 Epidemiology of periodontal diseases

Epidmiology is defined by Lilienfeld as the study of the distribution of diseases or a physiological condition in human populations and the factors that influence this distribution. [18]

Based on this definition, epidemiology research in periodontology should determine [19]:

(1) Prevalence of periodontal diseases in different populations.

(2) Elucidate an etiology and determinants of the development of these diseases.

(3) Provide documentation concerning the effectiveness of preventive and therapeutic measures aimed against these diseases on a population basis.

Periodontal disease is one of the two major dental diseases that affect human populations worldwide. [20]

The basic clinical measures for periodontitis, apart from gingival bleeding and radiographic assessment of bone loss, are clinical attachment loss (CAL) and probing depth (PD).

The WHO introduced the Community Periodontology Index (CPI) [21] to provide profiles of periodontal health status in countries, facilities comparisons and to enable countries to plan intervention programs for effective control of periodontal disease. Although this index has certain shortcomings when used as a stand-alone means of assessing the extent and severity of periodontal disease [20] it has been widely used for descriptive periodontal epidemiologic studies and needs assessment in developed and developing countries. [22]

Petersen and Ogawa 2005 [22] conclude that gingival bleeding is highly prevalent among adult populations in all regions of the world and advanced disease with deep periodontal pockets (>6 mm) affects about

10% to 15% of adults worldwide. Moreover, evidence shows that important risk factors for periodontal disease include poor oral hygiene, tobacco use, excessive alcohol consumption, stress, and diabetes mellitus. Integrated preventive strategies based on the common risk factors approach are recommended for public health practice. [23]

Chronic periodontitis:

According to the Armitage classification [24], "Chronic" periodontitis refers to progression of the disease over time without treatment and does not suggest that the disease is "untreatable."

Chronic periodontitis is characterized as occurring mostly in adults, but it can be seen in younger people. Destruction is consistent with the amount of plaque present and other local factors (i.e., anatomic and other factors that retain plaque next to a tooth such as overhanging restorations, open contacts and palato-radicular grooves); subgingival calculus is also commonly found. In general, the disease progresses slowly but there may be bursts of destruction. In addition, the rate of disease progression can be modified by local factors, systemic diseases and such extrinsic factors as smoking.

Chronic periodontitis has been further classified as localized or generalized depending on whether < 30% or > 30% of sites are involved. Severity is based on the amount of clinical attachment loss (CAL) and is designated as slight (1-2 mm CAL), moderate (3-4 mm CAL) or severe (> 5 mm CAL).

2.2.2 Pathogenesis of periodontal diseases

Page and Schroeder 1976 [25] classified the development of the disease into the "initial", "early",

“established”, and “advanced” lesions.

The initial lesion:

The “initial” lesion occurs 2–4 days following the beginning of plaque accumulation. The lesion is subclinical and can only be seen histologically. It is characterized by the formation of edema manifesting as an increase in gingival crevicular fluid (GCF) flow, an accumulation of polymorphonuclear neutrophils (PMNs) and loss of connective tissue.

Streptocooci are among the first organisms to colonize the acquired pellicle as plaque develops. These organisms produce a range of enzymes and metabolic end products which increase the permeability of the junctional epithelium, allowing both the ingress of further bacterial products and at the same time the outflow of GCF. [26]

The early lesion:

The early lesion develops after approximately 4–7 days of plaque accumulation. At this stage the nature of the developing lesion changes from one consisting primarily of PMNs to one with increased numbers of lymphocytes and macrophages. Vascular changes become more pronounced. As a result, there is a net increase in the flow of fluid into the affected gingival tissues, and a subsequent increase in the flow of GCF. The nature of the GCF at this stage changes from that of interstitial fluid to that of an inflammatory exudate, in other words edema. [26]

Established or progressive lesion:

The established/progressive lesion is primarily a lymphocyte/plasma cell lesion with the main identifying feature being the predominance of plasma cells within the periodontal connective tissues [27],[28] . The majority of lymphocytes are immunoglobulin bearing B-cells, although up to 30% of the lymphocytes may be T-cells. While the gingivally confined T-cell lesion remains relatively stable, this B cell / plasma cell lesion progresses and leads to the development of a periodontal pocket. Connective tissue breakdown leads to loss of the connective tissue attachment to the tooth and as a result the junctional epithelium migrates in an apical direction, thus forming a periodontal pocket. This in turn becomes lined by pocket epithelium with an ingrowth of rete pegs into the surrounding connective tissue. This is common to all chronic inflammatory lesions and is an attempt by the lesion to wall off from the surrounding tissues. Indeed, in periodontitis irrespective of the depth of the pocket, the underlying alveolar bone and periodontal ligament do not become inflamed. [29]

Advanced lesion:

The advanced lesion has essentially the same cellular features as the established lesion. The main difference lies in the overt loss of attachment that is evident clinically and histologically. It is now generally accepted that the mechanism of tissue destruction is via the effects of the host's immune response [30] and is not a direct consequence of the bacteria per se. Macrophages are not a dominant feature of the advanced lesion, comprising fewer than 5% of the cells. Fibroblasts when stimulated by the inflammatory cytokines IL-1, IL-6, TNF-α, and its fragments become denatured in the extracellular environment or are phagocytosed by surrounding fibroblasts. As the lesion advances, alveolar bone loss becomes apparent. However, the non-infiltrated fibrous band remains adjacent to the crestal bone, effectively encapsulating the progressing lesion and walling it off from the surrounding tissues. It should be noted again that underlying bone and periodontal ligament remain non inflamed. [29]

2.2.3 Risk factors for periodontal disease

Extensive epidemiologic and experimental evidence exists for the role of several risk factors in the initiation, progression, and severity of periodontal disease. A risk factor can be defined as an occurrence or characteristic that has been associated with the increased rate of a subsequently occurring disease. It is important to make the distinction that risk factors are associated with a disease but do not necessarily cause the disease. The term risk factor may indicate an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is known to be associated with disease related conditions based on epidemiologic evidence. Risk factors may be modifiable or non-modifiable. Modifiable risk factors are usually environmental or behavioral in nature whereas non-modifiable risk factors are usually intrinsic to the individual and therefore not easily changed. Non-modifiable risk factors are also known as determinants. [31]

There are several well recognized risk factors for chronic periodontal diseases like gender, smoking, alcohol (lifestyle), diabetes, obesity and metabolic syndrome, stress and genetic factors, osteoporosis, as well as deficiency in dietary calcium and vitamin D.

Beck et al 1994 [32] discussed the principles of the risk assessment process which consists of the following four steps:

1. The identification of one or several individual factors that appear to be associated with the disease.

2. In case of multiple factors, a multivariate risk assessment model must be developed that discloses which combination of factors most effectively discriminates between health and disease.

3. The assessment step, in which new populations are screened for this particular combination of factors, with a subsequent comparison of the level of the disease assessed with the one predicted by the model.

4. The targeting step in which exposure to the identified factors is reduced by prevention or intervention and the effectiveness of the approach in suppressing the incidence of the disease is evaluated.

Diabetes mellitus is considered a risk factor for periodontal disease as it is considered a factor that may modify the host's susceptibility to periodontitis and the disease's clinical phenotype including its extent, severity, progression, and response to therapy.

The relationship between diabetes and periodontitis has been discussed in the literature for over 70 years.

Because the inter-relationship between diabetes and periodontal disease applies in both directions it is called a bidirectional (two-way) relationship. [33]

Emrich et al 1991 [34] concluded an extremely high prevalence of type 2 diabetes of about 40–50% associated with periodontal diseases.

Genco et al 2000 [35] identified from Meta-analyses a statistically significantly higher mean clinical attachment loss of 1 mm (95% confidence interval: 0.15–1.84; P = 0.021) and a greater mean periodontal probing depth of 0.46 mm (95% confidence interval: 0.01–0.91; P = 0.046) in individuals suffering from type 2 diabetes mellitus compared with control subjects.

2.2.4 Gingival Crevicular Fluid

Gingival crevicular fluid (GCF) is considered as a serum transudate with a continuous flow out of the gingival sulcus, even under clinically healthy conditions [36]. In gingivitis the composition of gingival crevicular fluid changes to an exudate with increased levels of microbial and host-derived substances e.g. proinflammatory cytokines (such as interleukin-1b, interleukin-6, prostaglandin E2 and tumor necrosis factor-a), immune cells and enzymes released by resident and recruited cells representing the local inflammatory reactions. [37]

GCF can be collected from the gingival crevice surrounding the teeth. As such, the fluid reflects the constituents of serum, the cellular response in the periodontium, and contributions from the gingival crevice.

Lalla and Papapanou 2011 [33] concluded that periodontitis aggravates the metabolic control of patients with type 2 diabetes mellitus.

Grossi and Genco 1998 [38] mentioned that proinflammatory cytokines released locally in the periodontal tissues may enter the bloodstream and thereby influence distant tissues and organs. In contrast, increased systemic levels of proinflammatory cytokines involved in diabetes may influence the local conditions and immune reactions in periodontal tissues. The cytokines most frequently investigated were interleukin-1b and interleukin-6.

In patients with type 2 diabetes mellitus and chronic periodontitis, the levels of interleukin-6 in gingival crevicular fluid were reported to be significantly elevated in nearly all investigations. [39], [40], [41], [42] whereas only a few studies suggested no difference compared with systemically healthy control patients. [43], [44]

Sonnenschein and Meyle 2000 [45] concluded in their review that inconsistent outcomes were reported for gingival crevicular fluid interleukin-1b levels in type 2 diabetes mellitus and chronic periodontitis: some authors found elevated levels of interleukin-1b in the gingival crevicular fluid of patients with type 2 diabetes mellitus [39], [41], whereas a similar number of studies reported no statistically significant differences between groups. [46], [47]

2.3 Review of the link between diabetes and periodontal disease.

2.3.1 Role of diabetes mellitus in periodontal diseases

Diabetes mellitus and periodontal disease are both multifactorial diseases with a high prevalence worldwide. Diabetes mellitus play a crucial role in the pathogenesis of periodontitis. Evidence has consistently indicated that diabetes is a risk factor for increased severity of gingivitis and periodontitis[48]. Inflammation is a central feature of both diabetes and periodontal disease. Moreover, inflammatory processes are upregulated in the periodontal tissues of patients with diabetes.

Many diabetic complications may be associated with elevation of inflammatory pathways. Hyperglycemia can result in increased inflammation, oxidative stress, and apoptosis, and hence contribute to enhanced periodontal destruction. [49]

The increased levels of proinflammatory mediators in patients with diabetes contribute to more severe periodontal disease.

Another line of evidence suggests that a hyperactive inflammatory response to bacterial challenge is responsible for an enhanced severity of periodontal disease in patients with diabetes mellitus. [50]

It does not appear that the microbial flora of people with diabetes differs markedly from the microbial flora of those with no diabetes. [51]

Consideration should also be given to the role of advanced glycation end-products and of receptors for advanced glycation end-products. The receptors for advanced glycation end-products are elevated in patients with diabetes. This is important because the interaction of these receptors with advanced glycation end-products plays a role in the development of diabetic complications such as cardiovascular disease and kidney disease. [52]

There is an alteration in the capacity for repair in periodontitis associated with diabetes. Patients with diabetes have increased apoptosis, which is associated with delayed wound healing. [53]

There are also altered native immune responses in patients with diabetes. Patients with diabetes have been shown to have impaired neutrophil chemotaxis

Furthermore, diabetes may lead to increased severity of periodontal disease as a result of defective neutrophil apoptosis [54] and this, in turn, could lead to increased retention of neutrophils in the periodontium, resulting in increased tissue destruction as a result of the release of reactive oxygen species and histolytic enzymes from neutrophils. [55]

2.3.2 Role of periodontal diseases in diabetes mellitus

Periodontitis may be a risk factor for worsening glycemic control among patients with diabetes and may increase the risk of diabetic complications by increasing the level of proinflammatory and prothrombotic mediators in serum. [56]

Moreover, it is possible that systemic inflammation associated with the local inflammatory response triggered by periodontal microflora leads to insulin resistance. For example, TNF-a, which is elevated in the plasma of patients with periodontitis [57] is known to promote insulin resistance by interfering with insulin signaling. [58]

There is increasing evidence that systemic inflammation results from the entry of oral microbial agents and their virulence factors into the circulation. This is evidenced by elevated serum levels of C-reactive protein and other acute-phase reactants and raised biomarkers of oxidative stress. [59]

It is therefore biologically plausible that non-resolving chronic inflammation derived from periodontal

disease impacts on diabetes control (elevated HbA1C) and complications, as well as beta-cell function, insulin resistance and development of type 2 diabetes.

Some observational studies regarding the association between periodontal diseases and the risk for Diabetes mellitus complications have given strong evidence for this association.

Thorstensson et al 1996 [60] observed a significantly higher prevalence of proteinuria and cardiovascular complications such as stroke, transient ischemic attacks, angina, myocardial infarction and intermittent claudication in patents with severe periodontitis than in patients with gingivitis or mild periodontitis. These findings suggest that an association between renal disease, cardiovascular disease and its complications and severe periodontitis seems to exist.

Hayashi et al 2017 [61] observed within the limitation of their pilot study that periodontal treatment may be effective not only in improving metabolic control, but also in reducing the risk of diabetic kidney and liver disease in patients with type II diabetes mellitus.

2.3.3 The influence of periodontal treatment on glycemic concentration

Reduction in HbA1C is an established outcome measure of successful diabetes treatment. Periodontal therapy appears to be able to reduce systemic inflammatory mediators, such as C- reactive protein, tumor necrosis factor-a, interleukin- 6, and others, as well as to increase adiponectins in individuals with diabetes [62]. The reduction of these inflammatory mediators by periodontal treatment may result in increased insulin sensitivity with improved control of glycated hemoglobin. In turn, this improvement in glycated hemoglobin can lead to a reduction in the complications of diabetes mellitus that are associated with periodontitis, including cardiovascular and renal complications. [63]

Evidence derived from RCTs show that periodontal treatment results in a mean reduction in HbA1C of

0.4% at 3 months, but in that review, periodontal therapy of any kind (non-surgical or surgical periodontal therapy with or without the use of adjunctive antibiotics) were included. [64]

A recent systematic review shows moderate reduction in HbA1c after the non-surgical therapy in patients with type 2 diabetes. The strength of this meta-analysis is the restriction to non-surgical periodontal treatment alone, without the adjunctive antibiotics which could interfere with the mean change of HbA1c[65].

The American Academy of Periodontology /European Federation of Periodontology workshop report had two authors and 22 collaborators [66] and their statement about the reduction in HbA1c from scaling and root planning when it is performed every three months being equivalent to adding a second oral diabetes medication speaks volumes. As important is their statement that there is a dose-dependent relationship between periodontitis and diabetes complications. If such reductions following periodontal therapy can be sustained over the longer term, then this may contribute to reduced diabetes-associated morbidity and mortality.

Moreover, there was a clear guideline from the EFP/AAP Workshop to physicians and other medical health professions in Diabetes Practice which included educating the patient about the importance of receiving a thorough oral examination and particularly a comprehensive periodontal examination.

The take home message about the bidirectional relationship between diabetes and periodontal disease is the need for dental and medical professionals to collaborate to ensure overall health for each individual.

2.3.4 Early detection of prediabetes and undiagnosed T2DM

Since any marker of abnormal glucose metabolism is associated with an increased risk of progression to diabetes and/or cardiovascular disease, it can be argued that a single abnormality is sufficient for admission into a risk category, which the American Diabetes Association (ADA) has labelled ‘pre-

diabetes'. [8]

Pre-diabetes is a condition where blood-glucose levels are above the normal, but still do not qualify for the type II diabetes diagnosis. This condition, which is a precursor of manifest type II diabetes, is also known as impaired glucose tolerance.

Type 2 diabetes has an insidious onset with a long latent period of dysglycaemia. By the time, the diagnosis of diabetes is made, diabetes-related tissue damage occurs in nearly half of the patients. Even after diagnosis, the glycemic control is suboptimal in more than 50%, leading to the vascular complications. [8]

Evidences suggest that early detection of diabetes by appropriate screening methods, especially in subjects with high risk for diabetes will help to prevent or delay the vascular complications and thus reduce the clinical, social and economic burden of the disease. [8]

Moreover, the majority of type 2 diabetic subjects remain asymptomatic and opportunistic screening for diabetes would be required for the early diagnosis of the disorder. [67]

Tsai *et al*. 2002 [68] recognized that among those affected by diabetes, patients with poor glycemic control are at a higher risk for presenting with severe periodontitis which can be detected in dental clinic.

Moreover, Harrison *et al*. 1983 [69] and Ueta et al. 1993 [70] concluded that poorly controlled or undiagnosed/untreated patients with diabetes may present with or experience recurrent periodontal abscesses.

Patients generally visit their dental provider more frequently than their physician. The impact of diabetes screening and referral of patients with positive test results to their physician for management would have

an immediate benefit for the individual and as well as the health-care system. Early diagnosis is critical to the lifespan and healthspan of individuals with diabetes.

Borrell et al 2007 [71] used their study which analyze NHANES III data to develop a predictive equation that can form the basis of a tool to help dentists determine the probability of undiagnosed diabetes by using self-reported data and periodontal clinical parameters routinely assessed in the dental office that individuals with a self-reported family history of diabetes, hypertension, high cholesterol levels and clinical evidence of periodontal disease bear a probability of 27-53% of having undiagnosed diabetes.

Li S. et al 2011 [72] suggested that dental providers consider using a clinical guideline that includes the following predictors: waist circumference, age, self-reported oral health, self-reported weight and self-reported race or ethnicity, as well as any additional information on periodontal status and family history of diabetes. This clinical guideline could help dentists identify patients with undiagnosed diabetes, resulting in the earlier identification of dental patients who require treatment for diabetes and, thus, reducing morbidity and health care costs.

Lalla et al. 2011 [73] developed from prospective data a simple and efficient protocol to identify people with undiagnosed prediabetes or diabetes. This revealed that two dental parameters (number of missing teeth and percent of teeth with deep periodontal pockets) were effective in correctly identifying the majority of cases of unrecognized dysglycemia. Dental parameters show a presence of $\geq$ 26% deep pockets or $\geq$ 4 missing teeth correctly identified 73% of true cases; the inclusion of an HbA1c $\geq$ 5.7% increased correct identification to 92%.

Because of the close relationship between diabetes and periodontitis, it can be assumed that dental practitioners are extremely likely to encounter many patients having both diabetes mellitus and

periodontitis.

Due to the rapid recordings obtained, a glucometer can be used as an educational tool with the patient for easy and quick chair-side counseling.

Dental practitioners, however, may find the intraoral sampling technique more convenient as the sample can be obtained during routine scaling and the strip system provides a more objective indicator for referral to physicians than traditionally used medical history review and observation symptoms which suggest DM. [74]

Development of an intra oral blood sampling technique as opposed to the typically used finger site could make such tests even more suitable for use by dental practitioners [75] and allow for non-invasive way to screen blood glucose level in dental office. [76]

Parker et al. 1993 [77] tested the use of commercially available reagent strips and an in-home glucose monitoring device for the purpose of measuring glucose levels in gingival crevicular blood and found a very strong correlation was observed between gingival crevicular, capillary and venous blood glucose measurements.

Beikler T. et al 2002 [78] concluded from a pilot study that the values of blood samples taken from gingiva or fingertip showed a very high intrapatient correlation ($r=0.98$; $p<0.0001$).

Ardakani MR et al 2009 [79] concluded that, considering 50% of diabetics remain undiagnosed, testing sulcular blood may provide a suitable method for identifying potential diabetic patients during routine dental visits since there is a correlation with capillary blood. Appropriate referrals to a physician can then be made when warranted.

Parihar S. et al 2016 [80] observed a strong positive correlation (r) between glucose levels of GCB with

FSB and VB with the values of 0.986 and 0.972 in diabetic group and 0.820 and 0.721 in non-diabetic group. In addition, the mean values of GI and PPD were more in diabetic group than non-diabetic group with the statistically significant difference ($p < 0.005$).

3. AIM

Main objective:

- This study aims to assess if gingival crevicular blood collected during the diagnostic periodontal examination can be used as a blood source for glucometric analysis.

Specific objective:

- To compare Gingival crevicular blood glucose concentration with capillary finger blood glucose concentration.
- To test if gingival crevicular blood glucose concentration can identify undiagnosed diabetic or prediabetic patients who are unaware of their elevated blood sugar.

4. MATERIAL AND METHODS

Study Design

The design of this observational study followed the guidelines published by "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement", 2007 ([81])

Ethical Consideration

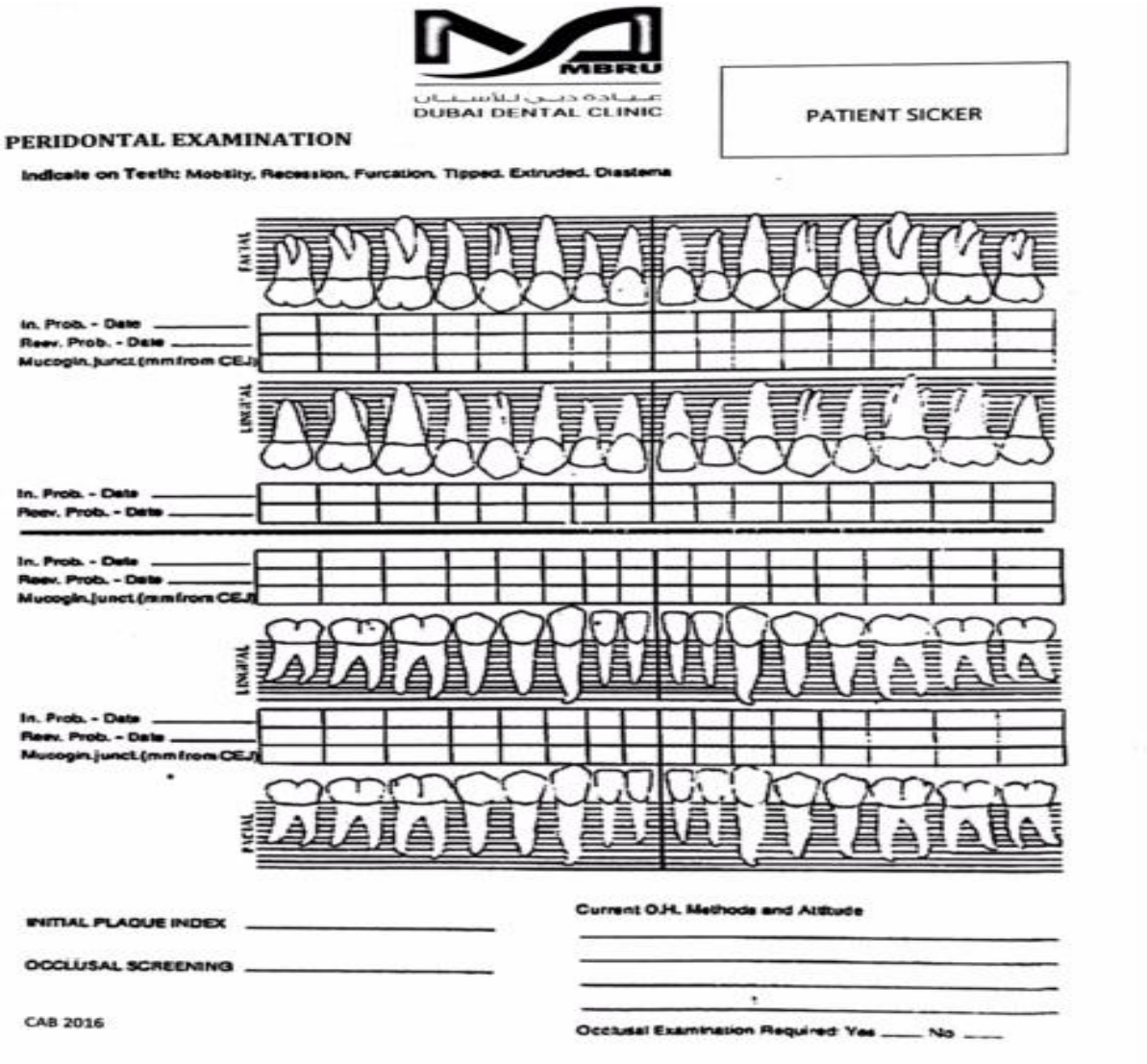
This study was conducted in full conformance with the principles of the "Declaration of Helsinki" [(82)], "Good Clinical Practice (GCP)" [(83)], and within the laws and regulations of the UAE/Dubai Healthcare Authority (DHCA). The ethical approval was obtained from the Research Ethics Committee in Hamdan Bin Mohammed College of Dental Medicine (HBMCDM). Appendix 1

Study Sample

A convenience sample of 40 adults patients (30-70 years) were invited to participate. 20 of them were healthy controls with no relevant medical history (Group I) and 20 were known diabetics (Group II) all were recruited from the Department of Periodontics, Dubai Dental clinic, Dubai, UAE. All subjects were verbally informed and a written informed consent was taken for participation in the study. Appendix2

Periodontal diagnosis:

As all patients were recruited from the Department of Periodontics in Dubai Dental Clinic, periodontal diagnosis was obtained from patients' files. Patients had been diagnosed after comprehensive periodontal assessment following the Armitage classification for periodontal diseases. Severity is based on the amount of clinical attachment loss (CAL) and is designated as slight (1-2 mm CAL), moderate (3-4 mm CAL) or severe (> 5 mm CAL). The following periodontal chart had been used.



Inclusion criteria:

- Patients with moderate to severe chronic periodontitis.
- At least one tooth in the maxillary anterior region showing bleeding upon probing.

Exclusion criteria:

- Patients requiring premedication or prophylactic drug regime, suffering from other systemic infection or diseases except diabetes.
- A periodontal pocket with suppuration.
- Subjects on medication that interferes with coagulation (e.g., anti-coagulants)
- Subjects taking supplemental vitamin C (ascorbic acid) that could interfere with the glucose test strip oxidation reaction.

Gingival crevicular blood glucose concentration (GCB) measurement:

- The site selected was the gingiva around the upper anterior teeth as access is ideal.
- Supra and subgingival scaling was done at the selected donor site prior to GCB measurement in order to remove food debris and plaque.
- Contamination with saliva was minimized by using gauze and cotton rolls placed in the upper labial sulcus.
- A UNC-15 periodontal probe was gently passed along the gingival sulcus to induce bleeding then the glucometer strip was placed in contact with the blood.
- The gingival crevicular blood glucose (GCB) concentration was recorded using an Accu–Chek Performa self-monitoring device (Roche Diabetes Care GmbH, Snadhofer Strasse 116, 68305 Mannheim, Germany).

- It took an additional two minutes of the patient time without any disturbance to the planned clinical treatment.

Capillary finger-stick blood glucose level (CFB) measurement:

- The soft surface of the fingertip was wiped with surgical spirit and the spirit was allowed to evaporate.

- The surface of the finger was then punctured with a sterile lancet and the blood drop was allowed to be drawn into the test area of the strip.

- The capillary blood glucose concentration was recorded using an Accu–Chek Performa self-monitoring device (Roche Diabetes Care GmbH, Snadhofer Strasse 116, 68305 Mannheim, Germany).

Both samples from each individual were taken at the same visit. The time of collecting blood from both sources were determined between 2:00 to 4:00 pm to control diurnal variation. The result from the Accu–Chek Perform self-monitoring device was used to compare gingival crevicular blood glucose concentration and Capillary finger blood glucose concentration. No blood samples were transferred to any laboratory outside the clinical room.

Statistical Analysis

The collected data were transferred to computer spread sheets and analysed using computerized Statistical Package for Social Sciences (SPSS, version 20, Chicago, SPSS Inc). Descriptive statistics were performed for the general description of the data. Chi-square and Exact Fisher test were performed to examine differences between categorical data and t-test was carried out to compare continuous variable. The level of statistical significance was set at 5%. A *p*-value of < 0.05 was considered significant in all statistical analysis. Linear regression was used to explain the correlation between gingival crevicular blood glucose concentration and Capillary finger blood glucose concentration.

5. RESULTS

The study sample included a total of forty patients, 20 were healthy controls with no relevant medical history (Group I) and 20 were known diabetics (Group II). The overall mean age (SD) was 42.5years (10.3). The mean age for Group I was 39.5years (9.8) and for Group II 45.5years (10.2). No significant difference was found between the two groups. The mean age and gender distribution of Group I and Group II are shown in Table 2.

Table 2: Gender and mean ages of Groups I & II.

	Gender		Age in years
	Male	Female	Mean (SD)
Group I	11	9	39.5 (9.8)
Group II	14	6	45.5 (10.2)

t test 1.88, P=0.068, NSS.

Regarding the periodontal diagnosis, in group I, 13 (65%) had been diagnosed with chronic moderate periodontitis while 7 (35%) with chronic severe periodontitis. In Group II, 11(55%) had been diagnosed with chronic moderate periodontitis and 9 (45%) with chronic severe periodontitis. (See Table 3)

Table 3: Periodontal diagnosis Groups I & II.

	Periodontal diagnosis	
	Moderate periodontitis	Severe periodontitis
Group I	13(65%)	7(35%)
Group II	11(55%)	9(45%)

The overall mean duration of diabetes in group II subjects was 5.7years (3.2). The mean of diabetes duration in patients with moderate periodontitis was 5.54years (2.44) while in patients with severe periodontitis 5.86years (3.98). Duration of diabetes with severity of periodontal diseases was not significantly correlated.

Table 4: Duration of diabetes and periodontal diagnosis.

	Periodontal diagnosis	N	Mean (SD)
Diabetes duration	Moderate	11	5.54 (2.436)
	Severe	9	5.86 (3.976)

The Shapiro-Wilk test confirmed that the data was normally distributed hence parametric tests were applied.

The finger capillary blood glucose concentration and gingival crevicular blood glucose concentration of Group I ranged between 86-148 mg/dL and 88-152 mg/dL, respectively. For Group II, the finger capillary blood glucose level and gingival crevicular blood glucose level ranged between 106-262 mg dL and 111-268 mg dL, respectively. (Figure4/ Figure5)

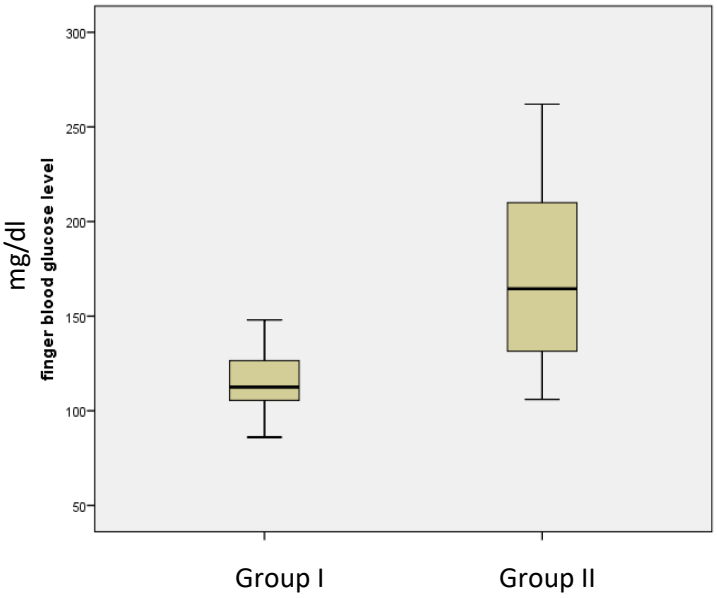


Figure 4: Range of capillary finger blood glucose concentration in Group I & II.

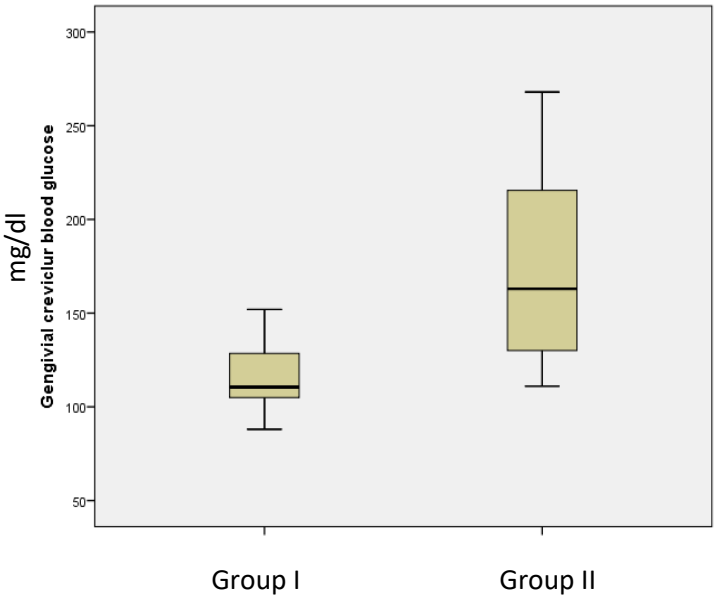


Figure 5: Range of gingival crevicular blood glucose concentration in Group I & II.

Within group I, the healthy controls, 5 of the 20 patients were identified with a blood glucose concentration of more than 140 mg/dl. These patients were referred to Dubai Diabetes Center (DDC) for further investigation to confirm their prediabetic status.

The mean capillary finger blood glucose concentration and gingival crevicular blood glucose concentration was 115.10(16.97) mg/dL and 116.30(16.67) mg/dL for group I, respectively. While in group II it was 172.10(47.04) mg/dL and 173.15(47.71) mg/dL, respectively. (See table 5)

Table 5 : Mean of capillary finder blood glucose concentration and gingival crevicular concentration in Group I & II.

	Mean (SD)	
	Capillary finger blood glucose mg/dL*	Gingival crevicular blood glucose mg/dL**
Group I	115.10 (16.97)	116.30 (16.67)
Group II	172.10 (47.04)	173.15(47.71)

* $t=5.031$, $p<0.001$ ** $t=5.098$, $p<0.001$

Comparison of mean figure blood glucose concentration between Group I and Group II was highly significant ($t=5.031$, $p<0.001$). Similarly, the mean gingival crevicular blood glucose was also significantly different between the groups ($t=5.098$, $p<0.001$).

There was a strong correlation between mean blood glucose from capillary fingers and gingiva (0.996; $p<0.001$) within each group.

The correlation between the glucose level from capillary finger and gingival crevicular blood has a strong linear relationship regardless of gender, age, periodontal diagnosis (either moderate or severe) and duration of diabetes within this sample.

Multiple regression analysis was carried out with the predictive independent variables as shown in Table 6. Gingival crevicular blood glucose was the dependent variable. Finger blood glucose concentration was highly predictive for gingival crevicular blood glucose concentration ($p<0.001$).

Table 6: Regression analysis.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	3.067	4.407		.696	.491
	Finger blood glucose level	.987	.016	.982	61.586	.000
	Age	.115	.076	.026	1.514	.139
	Gender	-2.625	1.356	-.029	-1.936	.061
	Periodontal diagnoses	.347	1.484	.004	.234	.816
a. Dependent Variable: Gingival crevicular blood glucose						

A further linear regression model with gingival crevicular blood glucose as the dependent variable and diabetes duration, age and gender as predictive variables was carried out. Diabetes duration was highly predictive for gingival crevicular blood glucose concentration ($p<0.001$). (See Table 7)

Table 7. Linear regression analysis model in Group II

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	117.494	39.179		2.999	.008
	Age	.447	.741	.096	.603	.555
	Gender	-24.185	13.829	-.255	-1.749	.099
	Diabetes Duration	12.250	2.537	.760	4.829	.000
a. Dependent Variable: Gingival crevicular blood glucose						

6. DISCUSSION

In the present study, a total number of 40 patients were recruited from the Department of Periodontics, Dubai Dental Clinic (20 healthy control group and 20 in the diabetic group). Capillary finger and gingival crevicular blood was used as sites for blood collection to estimate the glucometric status. There was a strong correlation between capillary and gingival crevicular blood glucose concentrations which was highly statistically significant. (0.996; $p<0.001$).

The results of the current study are similar to the findings of previous studies. Nemma S. et al found a positive correlation between CFB and GCB in a diabetic group ($r = 0.943$) as well as a non-diabetic group ($r = 0.926$) [(76)]. Another study shows a very strong correlation ($r = 0.97$) between CFB and GCB, which was statistically highly significant ($P < 0.0001$). [(84)]

Other studies by Stein et al. [(85)] and Tsutsui et al. [(74)] to the more recent studies of Beikler et al. [(78)] and Khader et al. [(86)] have attempted to show that blood from the gingival crevice due to inflammation can provide an acceptable source for measuring blood glucose in patients with diabetes.

Parker et al [(77)] who examined patients with diabetes and unknown periodontal status, observed a very strong correlation between gingival crevicular, capillary and venous blood glucose measurements. Ponni et al. [(87)] found a strong correlation between gingival crevicular fluid, finger prick and venous blood ($r = 0.99$, $P < 0.001$).

In the current study venous blood was not tested as simple screening was the study's aim with follow up use of venous blood if there was any concern, when referred to a diabetic center. While venous blood samples used for diabetes mellitus screening are the gold standard, gingival crevicular blood may prove to be a more practical approach for routine dental office screening for diabetes mellitus in periodontal

patients.

Giving the current understanding of the close relationship between diabetes and root caries it has been suggested that diabetes risk assessment should include gingival crevicular blood glucose measurement in patients with root caries. [88]

In the current study, gingival crevicular blood glucose showed a slightly higher mean value than finger prick capillary blood glucose, in contrast with another study with the opposite result. This was believed to be due to contamination of gingival crevicular fluid diluting the glucose concentration producing lower measurements in gingival crevicular blood. [89]

The method of collecting gingival crevicular blood is critical because the glucose concentration may be altered if there is any contamination from saliva and oral debris. For this reason, Neema S. et al used capillary tubes to collect gingival crevicular blood instead of wiping blood directly from the gingiva [76]. In the current study efforts were made to minimize the contamination by removing all plaque and food debris, and by applying cotton rolls in the labial vestibule and were able to minimize saliva contamination by following this protocol. The result shows slightly higher glucose concentration in gingival crevicular blood which confirms that we can use test strips directly without any need for other instruments.

Moreover, in this study diurnal variation was controlled by testing glucose concentration from both sites at a specific period of time between 2:00 – 4:00 pm. Diurnal variation forms an important part of the diabetes literature because of its impact on diabetes diagnosis and medication time.

Troisi RJ et al [90] observed the impact of diurnal variation in fasting plasma glucose in patients examined in the afternoon. They concluded that if current diabetes diagnostic criteria are applied to patients seen in the afternoon, approximately half of all cases of undiagnosed diabetes in these patients will be missed. In

the present study, random blood glucose concentration was measured, not fasting blood glucose, but diurnal variation should be controlled.

In the current study, we found that Diabetes duration was highly predictive for gingival crevicular blood glucose concentration ($p<0.001$).

There was no significant correlation found between the severity of periodontal diseases and duration of diabetes mellitus in our study. This might be because all study subjects in Group II had controlled diabetes. Moreover, by not including mild periodontitis, the relationship between periodontal severity and duration of diabetes may have been skewed.

Rajahans et al [(91)] conclude that poorer the glycemic control, and longer the duration of diabetes, the greater will be the prevalence and severity of periodontal disease.

As an incidental finding in the present study, five out of twenty healthy controls were identified with a blood glucose concentration of more than 140 mg/dL. These patients were referred to The Dubai Diabetes Center (DDC) for further investigation to confirm their prediabetic status. This incidental finding has also been seen in other studies. Parihar S. et al 2016 [(80)] found 4 subjects were diagnosed as new diabetic patients. Harmanpreetkure et al. also found 3 patients showed potential diabetes. These two studies used a venous blood source for glucose measurement in a laboratory glucose analyzer to compare it with capillary finger and gingival crevicular blood concentration level. In the current study we relied on both capillary finger and gingival crevicular blood to measure blood glucose level and were able to identify subjects with undiagnosed prediabetes.

Almost half of the adult patients attending PHC clinics in Abu Dhabi had undiagnosed T2DM, or increased diabetes risk. The independent predictors of undiagnosed T2DM were age and BMI ≥ 25 [92]

Evidence suggests that periodontal changes are the first clinical manifestation of diabetes. Moreover, a thorough meta-analysis by Papapanou demonstrated that a majority of studies which included nearly 3500 diabetic adults showed a more severe periodontal destruction in diabetic adults than in adults without diabetics [93].

Thus, periodontal diseases may be considered it as a predictor of undiagnosed T2DM and perdiabetes. Moreover, oral health care providers can have a significant, positive effect on the oral and general health of patients with diabetes mellitus. As part of the Ministry of Health plan to reduce the prevalence of the disease from 19 per cent of the population to 16 per cent by 2021, dental practitioners should be involved in achieving this target.

In the present study, 5 nondiabetics were found to have a high glucose concentration and were diagnosed as prediabetic patients. It is a bonus to identify patients at this stage as their diabetic status is reversible. The American College of Endocrinology Pre-Diabetes Consensus Conference [94] suggested the following approach to manage prediabetes:

- Self-monitoring of food, drink, and exercise.

  By increasing patients' awareness of behavior, measuring their progress, improving compliance with behavior change, and identify sources of excess calories.

- Goal setting.

  By helping patients establish realistic antecedent goals by limiting restaurant meals; reducing the rate of food consumption; setting goals for calorie, fat, and activity levels; and establishing consequence goals for relapse prevention and rewards. Goals need to be specific, manageable, and

attainable.

- Stimulus control.

  It is important to increase cues for healthy eating and exercise and to decrease cues for overeating and inactivity.

- Cognitive strategies.

  An important aspect of the curriculum is the restructuring of maladaptive thought patterns to eliminate the idea of "failing."

- Social support.

  Perception of support correlates with weight loss, and including spouses in a program modestly improves success, with successful supporters particularly helpful in participants' achieving goals.

- Reinforcement of success.

  It is important to reward behavior as soon after the accomplishment as possible. Even if without weight loss, what was done correctly should be identified and the patient should be congratulated.

With this approach and with the possible need for medication, prediabetes can be managed in a simple way with decreasing the risk of the mortality and morbidity associated with T2DM.

This study has shown the potential for the use of a simple, intra-oral, screening tool in identifying undiagnosed diabetes and prediabetes and its acceptance could potentially lead to the screening of all dentals patients who exhibit bleeding on probing.

According to the limitations of this study, it was including small sample size (20 subjects in each group) and there was no age matching: in the diabetic group the mean age was 6 years older than control group and this was nearly significant. Moreover, it was not a representative sample as it was confined to patients attending one dental clinic without involving diabetic centers, no gender matching (more males than females) .

7. CONCLUSIONS and RECOMMENDATIONS

It can be concluded that:

- A strong and statistically significant correlation (0.996; $p<0.001$) was found between capillary finger blood glucose concentration and gingival crevicular blood glucose concentration.
- Gingival crevicular blood can be used as a blood source for glucometric analysis and will allow for a non-invasive method to screen blood glucose concentration in the dental office.
- Gingival crevicular blood glucose can be measured with the Accu-Chek® Performa safely and easily to screen for diabetic status in patients with bleeding on probing.

Recommendations:

- Oral health providers can play a crucial role with minimal cost and time in identifying undiagnosed diabetic patients. Diabetes Centers in the United Arab Emirates achieve a very high standard of care. There appears to be, however, a lack of knowledge within healthcare providers of the role of dentists in the care of diabetic patients. A multidisciplinary is recommended in the care of these patients. Good collaboration between all health care providers including dentists is crucial in order to achieve the best care pathway possible.

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9. APPENDICES

APPENDIX 1 :

Date: 30/11/2016

Dear Dr Asmaa Khailefah Perio Resident

Re: Your research protocol

Titled: Gingival crevicular fluid .....

Thank you for submitting your revised research protocol to the Research and Ethics committee of the Hamdan Bin Mohammed College of Dental Medicine, MBRU.

It was originally considered at the meeting held on: 23/10/2016

I agree to approve the protocol. Please make sure you see your research supervisor regularly during the project in order to maintain close collaboration and support. The committee would like to remind you that it is a requirement of the programme that you complete a research dissertation, which comprises 15% of credits within the 3-year MSc programme.

With best wishes

Yours sincerely,

Prof A Milosevic

Chair, Research and Ethics Committee, HBMCDM

APPENDIX 2 :

Informed Consent Form

Principal Researcher Asmaa khaliefah Alahmoudi .

Title of project: A study to evaluate gingival blood as a screening tool for blood glucose concentration

Purpose of the project: You are being asked to participate in a research study examining the crevicular blood glucose level .

Patient Selection: All Adults (healthy and diabtetic) patients who attended periodontology clinic in Dubai dental clinic will be asked to be screened to examine blood glucose level of bleeding gum (around front tooth) and it will take about 2 minutes of your time.
Participation in this study is completely voluntary, if you decide not to participate there will not be any negative consequence.

Research steps: on the day of appointment with your periodontist and as usual they will measure your blood sugar by finger prick, then when you will be on the dental chair you will be asked after scaling procedure to collect blood from your bleeding gum.

Potential risks/Benefits: No foreseeable risks are involved in this study / We expect the project to benefit you to know blood glucose level without additional finger prick.

Confidentiality: Your examination records to this study will be completely anonymous, and only the investigators will have access to the research data. The confidentiality of your individual information will be maintained in any publications or presentations regarding this study.

If you have any questions about this study, feel free to contact:

Name: Dr.Asmaa khaliefah.

Address: Dubai Dental clinic-DHCC

E-mail: Asmaa.kaleifah@mbru.ac.ae

By signing this form, I am attesting that I have read and understand the information above and I freely give my consent to participate in this study.

Printed name of Research Participant: Date reviewed & signed: Signature:

Investigator Name: Signature: