

## Existing Opinions on the Correlation between Blood and Salivary Glucose Concentrations for Diagnosis and Monitoring of Diabetes Mellitus

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### Abstract

Diabetes mellitus is defined as a group of chronic metabolic diseases that are characterized by chronic hyperglycemia and other related metabolic disturbances. It is caused either by relative/absolute insulin deficiency or cellular resistance to insulin action, or both. Due to delay in the diagnosis process, and fear of the disease and its investigative procedure by some patients, diabetes mellitus has become the major cause of death. The most commonly employed investigative procedure to diagnose diabetes mellitus and controlling glycemia is blood investigation. Unfortunately, the procedure is invasive, painful, and may cause discomfort to patients due to the need for frequent testing. Consequently, a noninvasive, much simpler, and painless procedure is very desirable. Saliva represents an attractive alternative sample and offers a distinct advantage as it can be collected noninvasively and easily without special skill, and is low cost. The present review has found more studies with a positive correlation between blood and salivary glucose concentrations than those with a negative correlation. The difference between these studies' findings may be attributed to the difference in study population and criteria of selection, samples (saliva and blood) collecting methods, analyzing methods, and influencing factors that should be considered before the test.

**Keywords:** Blood glucose, Diabetes mellitus, Diagnosis, Monitoring, Salivary glucose.

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### 1. INTRODUCTION

Diabetes mellitus is defined as a group of chronic metabolic diseases that are characterized by chronic hyperglycemia and other related metabolic disturbances such as dysregulation of carbohydrate, lipid, and protein metabolism. It is caused either by relative/absolute insulin deficiency (insufficient insulin secretion) or cellular resistance to insulin action, or both [1-6]. Diabetes mellitus can be classified into type 1, which consists of pancreatic beta cells destruction, causing insulin deficiency, affecting 5-10% of the diabetic population; type 2, which consists of a combination of decreased insulin secretion and decreased insulin sensitivity, affecting 90-95% of the diabetic population [4, 5, 7]; gestational diabetes mellitus; and other specific types of diabetes mellitus

[5,7]. Although all these types have chronic hyperglycemia as common characteristic, their etiology and pathogenesis are different [5].

Due to delay in the diagnosis process, and fear of the disease and its investigative procedure by some patients, diabetes mellitus has become the major cause of death [6]. The increased morbidity and mortality encountered in diabetic patients is mainly due to several complications of the disease [3]. The complications of diabetes mellitus include microangiopathies (retinopathy, nephropathy, and peripheral neuropathy), macroangiopathies (cardiovascular disorders), alterations in wound healing, oral cavity diseases, and other organ or systems disturbances, which may severely impact the patient's quality of life and shorten

his lifespan [1,2]. Timely identification, control, and stabilization of glycemia in diabetic patients play a major role to minimize the occurring risk of some of the aforementioned complications [2-5, 8].

The conventional and most commonly employed investigative procedure to diagnose diabetes mellitus and controlling glycemia is blood investigation through venous puncture and capillary venous puncture (finger puncture) for blood sample collections from patients and analysis of glucose and glycated hemoglobin (measure of average glycemic control over the past three months), using a variety of biochemical techniques. Unfortunately, the procedure is invasive, painful, and may cause discomfort to patients due to the need for frequent testing [1-3,5-10]. The home method for self-monitoring of blood glucose has been developed in the past few years, consisting to the use of Glucometer, but it is also an invasive and painful procedure because it requires a blood sample [2]. The invasive procedure may be associated with needle anxiety or risk of blood-borne infections or both. Fear of needle-sharp, resulting pain of the invasive procedure and frequent intervals of testing are physically and psychologically traumatic to the patient and can discourage some patients from monitoring their blood glucose levels regularly [1,5]. Almost two-thirds of diabetic patients (67%) avoid regularly monitoring their blood glucose levels due to the painful and invasive nature of the monitoring procedure [4]. Consequently, a noninvasive, much simpler, and painless procedure for preliminary diagnosis and self-monitoring of blood glucose concentration using other body fluids glucose concentration testing for estimation of blood glucose concentration is very desirable to help the diabetes mellitus patients to be free from some burden [1,4,10,11].

Saliva represents an attractive sample and offers a distinct advantage as it can be collected noninvasively and easily without special skill, involves fewer complications, and is low cost [3, 5-7, 10, 12]. It acts as a mirror of the body; it may reflect the body's health and serve as a partial filtrate of blood for monitoring the disease and health status [5, 7, 12]. Saliva can be used as a biomarker of preliminary disease detection that may lead to more effective diagnosis and treatment or monitor of local and systemic diseases, including diabetes mellitus [6, 10-12], because the components of saliva can be related to the hormonal, immunologic, neurologic, nutritional and metabolic state of the individual [10-12]. Most of the saliva components come from blood capillaries by diffusion, active transport, and/or ultra-filtration through the gingival sulcus [5].

Glucose is present in the saliva of non-diabetic patients as well as diabetic patients [1]. Due to its low molecular weight, it can easily move through the membranes of blood vessels membranes, passing from

the blood plasma to the gingival fluid, via the gingival sulcus, and then reach the saliva [4, 6, 11]. There are several studies in the literature about the usefulness of salivary glucose test as a noninvasive procedure in the monitoring of diabetes mellitus, which remains a matter of controversy. Some authors have found a correlation between salivary and blood glucose concentrations, and showed that salivary glucose levels were high in diabetes mellitus patients compared to non-diabetic patients, other authors reported different results [5, 7, 8, 11-14]. Other studies aimed to develop saliva-based tests for diagnosis and/or monitoring of systemic diseases such as diabetes mellitus [12]. After many decades of research on the subject, some questions still controversial: is it possible to estimate the blood glucose concentration from salivary glucose concentration? Is there any correlation between blood and salivary glucose concentrations? This review aimed to report the literature-based opinions on the correlation between blood and salivary glucose concentrations for diagnosis and monitoring of diabetes mellitus.

## 2. QUANTITATIVE MEASUREMENT OF BLOOD AND SALIVARY GLUCOSE

### 2.1. Blood glucose (Glycemia)

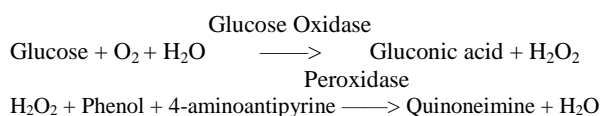
#### 2.1.1. Sample collection

Sample collecting for the estimation of blood glucose in laboratory is done using an invasive and painful method. The fasting glucose test is preferably done in the morning [7, 15], it is recommended to patients to keep the stomach empty at least 8 hours before the sample collection, and the post-prandial glucose test may be done at any time. Venous blood is collected to the sterile test tube [6, 7], centrifuged, and the obtained serum could be used immediately or kept frozen until use [7, 15].

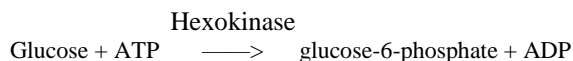
#### 2.1.2. Measurement methods

Several authors [16-18] have described different methods for estimating blood glucose, among which the most important are Glucose Oxidase-Peroxidase (GOD-POD), Hexokinase, and glucose dehydrogenase methods [16-21]. Blood glucose may be assessed in a laboratory (using a laboratory analyzer) or by the patient himself through a self-monitoring method (using a glucometer) [22, 23].

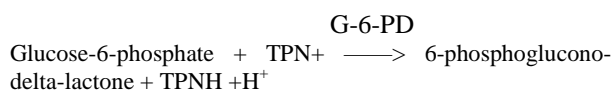
The GOD-POD method is simple to realize, linear and sensitive; and requires simple instrumentation [17, 18]. It is based on the oxidation of glucose into gluconic acid and hydrogen peroxide in a reaction catalyzed by GOD after which the peroxide itself is detected by using phenol (a chromogenic oxygen acceptor) and 4-aminophenazone, in presence of peroxidase (POD) to give a quinoneimine that forms a red complex which intensity is proportional to glucose concentration [6, 10, 20, 24].



Hexokinase method is based on the phosphorylation of glucose by adenosine triphosphate (ATP) catalyzed by hexokinase [16, 21]:



Glucose dehydrogenase method (Glucose-6-phosphate dehydrogenase) is specific for glucose and glucose-6-phosphate; it is based on the oxidation of glucose-6-phosphate by glucose-6-phosphate dehydrogenase in the presence of triphosphopyridine nucleotide (TPN) [16, 21]:



The self-monitoring method (using a glucometer) is used as an alternative to laboratory analyzers. It helps the patient to measure his blood glucose level, providing information about his individual dynamic blood glucose profile and understanding of the timing of his blood glucose variation [25]. The glucometer measures the glucose concentration in whole blood by using a glucose oxidase biosensor. It is often used to follow up the diabetic patient. However, for diagnosis and treatment purposes, it is advised to use laboratory analysis, as it was found that the glucometer has a poor validity and reliability compared to the laboratory analyzer [22].

Several factors such as diet, physical activities, treatment (Anti-Diabetic medicines, corticosteroids, etc.), acute infectious diseases (urinary tract infection, dental abscess, angina, bronchitis, etc.), and stress (infarction, trauma, accident, emotional shock, psychological problems, annoyances, etc.) may influence glycemia levels in diabetic patients [26].

## 2.2. Salivary glucose

### 2.2.1. Sample collection

Contrary to blood collection, collecting saliva is painless and noninvasive. The procedure is done 1-2 hours after breakfast [6]. Several methods are described for collecting the whole oral fluid or a specific saliva specimen [27-29]. Collecting the whole saliva is the easiest among them and can be performed even by a person without any specific training [30].

Some authors [6, 28-30] have suggested the following ways of the whole saliva sample collection:

- Saliva can be drained off or allowed to drip off from the lower lip;
- The subject can spit the saliva into a test tube;
- Saliva can be sucked up from under the tongue using a syringe.

After its collection, saliva should be centrifuged, aliquoted, and kept frozen until use [11, 27, 30].

### 2.2.2. Measurement methods

The measurement methods of salivary glucose are the same as those aforementioned for blood glucose [11, 13, 27, 30] except the fact that, after preparation, the tubes should be mixed with a vibrator for homogenization of the saliva and enzyme reagent [11].

However, salivary glucose can also be detected using other methods such as microfluidic paper-based devices ( $\mu$ PADs) and wearable devices methods [31], Smartphone-based non-invasive salivary glucose biosensor method [32], or the Smart Tongue Depressor-Based Biosensor method [33].

## 3. FACTORS INFLUENCING SALIVARY GLUCOSE CONCENTRATION

Although the saliva is easy to collect and manipulate, it is recommended to have careful attention when manipulating to reduce the variation in sample integrity because contamination of salivary samples (by blood samples) can affect the quantitative estimation of salivary glucose [30].

In normal conditions, adults can produce 0, 5 - 1,5L of saliva a day [34], but its flux and composition can be modified under some physiological and pathological conditions, such as stimulation, presence of food in the mouth, hormonal state, psychological state, drugs, age, oral hygiene, and physical exercise [34-36].

The salivary glucose concentration is inconsistent [6], it may be influenced by several factors:

- In diabetic patients, there may be an alteration in the basement membrane of blood vessels, which may lead to increased diffusion of glucose from blood to saliva, resulting to an increased salivary glucose concentration [5].
- Oral retention of alimentary carbohydrates [13], glucose utilization by oral bacteria [9], release of carbohydrates from salivary glycoproteins, and contamination of saliva by a large outflow of crevicular fluid in patients with a poor gingival status influence the salivary glucose concentration [13].
- The increase of salivary mucus content (mucopolysaccharide and glycoprotein) may also lead to an increased salivary glucose concentration [6].

- The increase of salivary amylase level due to hormonal or neural regulations under psychological and physical stress, which increase the breakdown of starch to glucose and increase salivary glucose concentration [5,6,9].
- The oral antimicrobial activity increases salivary hydrogen peroxide and may lead to overestimation of glucose concentration by GOD-POD (glucose oxidase-peroxidase) method [6,9].
- Infections such as candidiasis in patients with dentures or HIV and inflammation of salivary glands could increase the salivary glucose concentration [5].
- The salivary glucose concentration can be affected by the time and the method of saliva sample collection [5].
- Salivary glucose level decreases after beginning insulin treatment [5].
- Stimulation of saliva before sample collecting may give inaccurate values of salivary glucose because of increased dilution [3,8]. Unstimulated saliva has been reported in the majority of studies as reliable sample for estimating the salivary glucose concentration. This because stimulated saliva may give inaccurate values as the foreign substances used to stimulate saliva may lead to the alteration of pH and stimulation of the water phase of saliva secretion, which results in an increased dilution, and disturbance of glucose concentration [3].
- Lower levels of glucose in saliva compared to that in serum and capillary whole blood among diabetes patients could be influenced by the hydration, environmental factors, mood, and anti-diabetic drugs [9,12].
- Some comorbid conditions may also influence salivary glucose concentration [5].

#### 4. CORRELATION

##### Positive correlation

The earliest descriptions of correlation between blood glucose and salivary glucose levels were reported by Kortuem in 1944 [6, 37], Shannon *et al.* in 1960 [6, 38], Englander *et al.* in 1963 [6, 39], and Campbell in 1965 [6, 40]. A high number of studies [1, 3, 5-7, 10-15, 20, 24, 41-48] confirmed this positive correlation. Most of those studies have suggested that saliva can contribute as a simple, quick, and noninvasive method for screening of diabetes mellitus because the increase in blood glucose causes an increase in salivary glucose. The presence of glucose in the saliva of non-diabetic individuals as well as diabetic patients has been attributed to both paracellular and intracellular pathways [1]. The increased level of salivary glucose in diabetic patients may be explained by the fact that diabetes mellitus is often associated with alteration of basement membrane consisting to its increased permeability caused by other glucose products, such as diacylglycerol, sorbitol, and fructose-6-phosphate [3, 12]. This leads to the increased passage

of molecules from salivary glands into their secretions, resulting to an enhanced leakage of serum-derived components including glucose into the whole saliva via gingival crevices [3, 7, 12]. Among the authors who found a positive correlation, some [1, 3] have formulated equations to estimate blood glucose concentration from salivary glucose concentration when known.

##### Non-correlation

Many studies [2, 13, 49-52] found non-correlation between blood and salivary glucose concentrations. All those authors explained this non-correlation by some of the aforementioned factors influencing the salivary glucose concentration, which may limit its use as an indicator of glycemia in the monitoring of diabetes mellitus. Additionally, Twetman *et al.* explained this nonexistent correlation by the threshold mechanism in the salivary glands [51].

#### 5. CONCLUSION

There are more studies with a positive correlation between blood and salivary glucose concentrations than those with a negative correlation. The difference between these studies' findings may be attributed to the difference in study population and criteria of selection, samples (saliva and blood) collecting methods, analyzing methods, and influencing factors that should be considered before the test. The high frequency of studies with positive correlation leads us to conclude that there might be a correlation between the glucose concentrations of the two specimens. Despite this correlation, some authors suggest further studies on the topic before the effective use of salivary glucose test for diagnosis and monitoring, while others suggest its use for monitoring only. We believe at this stage of the research progress on salivary glucose test and its application in the management of diabetes mellitus, the test can be useful for monitoring only, but for diagnosis and treatment purposes, the glycemia test should remain the gold standard. To achieve the goal of using salivary glucose test for daily monitoring of diabetes mellitus, we recommend the development of self-monitoring devices using saliva as the glucometer uses blood. The test must always take into account factors that may influence salivary glucose concentration to avoid inaccurate measurement.

#### 7. ACKNOWLEDGEMENTS

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##### Conflict of Interest

There are no conflicts of interest to declare by any of the authors of the present study.

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