# Effect of Diabetes on Rat's Tongue Papillae

## *(Histological, Immunohistochemical And Image Analysis Study)*

**Thesis**

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**By**


## Marwa Abd-El Mohsen El Sheikh

***B.D.S (Cairo University)***



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**Cairo University**
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# Supervisors


## Prof. Dr. Amir Saad Gerges

**Professor and Chairman of Oral Biology Department**
**Faculty of Oral and Dental Medicine**
**Cairo University**

## Dr. Mona Hassan Farid

**Assistant Professor and Chairman of**
**Oral Biology Department**
**Faculty of Oral and Dental Medicine**
**El- Azhar University**

## Dr. Maha Hassan Besheer

**Assistant Professor of Oral Biology Department**
**Faculty of Oral and Dental Medicine**
**Cairo University**

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*To…*

*The Soul of My Father*

*My Mother*

*My Dear Husband*

*And My Two Lovely Daughters*

# Contents

# *INTRODUCTION*

# INTRODUCTION

Greek and Roman physician used the term “diabetes” to refer to conditions in which the cardinal finding was a large urine volume. “Mellitus” comes from the Greek word “sweet”. The Greeks named it thus due to the excessive amounts of diabetic urine which attracted flies bees because of its glucose content. (***Ganong, ١٩٩١***).

The ancient Chinese tested for diabetes by observing whether ants were attracted to a person’s urine. (***Ash, ١٩٩٢***).

Diabetes mellitus develops from either a deficiency in insulin production or impaired utilization of insulin. Based upon these two conditions, diabetes mellitus can be divided into two types: Insulin –dependant diabetes mellitus (IDDM) or type I, and non-insulin dependant diabetes mellitus (NIDDM) or type II diabetes (***Owen and Shuman, ١٩٩٠).***

Diabetes is in top ١٠, and perhaps the top ٥, of the most significant disease in the world. The Centers for Disease Control has termed the disease as an epidemic. (***Szybinski , ٢٠٠١).***

In ٢٠٠٤, according to the World Health Organization, more than ١٥٠ million people worldwide suffered from diabetes. Its incidence is increasing rapidly, and it is estimated that by the year ٢٠٢٥ this number will be doubled. Diabetes is common (especially Type ٢) in the more developed countries .In ٢٠٠٢ there were about ١٨.٢ million diabetics in the United States alone.

Diabetes mellitus (DM) represent a group of diseases of heterogeneous etiology, characterized by chronic hyperglycemia and other metabolic abnormalities which are due to deficiency of insulin effect. (***Kuzuya et al., ٢٠٠٢).***

Owing to its great importance, as being one of the most world wide spread disease, its effect on many organs and tissues had been studied, but little information in literature were found about its effect on the oral specialized mucosa.

# REVIEW OF LITERATURE

Diabetes mellitus is a medical disorder characterized by hyperglycemia (elevated blood glucose levels), especially after eating. Hypoglycemia (low blood glucose) is rare except as a side effect of treatment. ***(Nathan, ١٩٩٣***).

There are different types of diabetes mellitus, most of them are asymptomatic for some time after onset but all share similar symptoms and complications at advanced stages. (***Sherwin, ١٩٩٦***).

This disease is characterized by abnormalities in the metabolism of carbohydrate, protein and fat. It is often accompanied by specific microvascular, macrovascular and neuropathic complications. It is now recognized that diabetes mellitus include a group of genetically and clinically

heterogeneous disorders in which glucose intolerance is a common factor, thus its diagnosis depends on identification of specific plasma glucose abnormalities ***(Lebovitz, ١٩٨٤***).

Moreover diabetes is accompanied by glucosuria, oliguria, polydipsia and polyphagia, beside that hyperglycemia itself can lead to dehydration and ketoacidosis (***Sherwin, ١٩٩٦***). Longer term complications include cardiovascular disease (myocardial infarction), cerebral infarction, renal failure, retinal damage with eventual blindness, nerve damage and gangrene with probable loss of toes, feet and even legs. (***Kikkawa , ٢٠٠٠***).

Conversely , successful keeping blood sugar normal at all times, specially after eating by about ٤ hours, has been shown to reduce or prevent each of these problems .(***Myers , ١٩٩٤***).

## *Classification of diabetes mellitus*

### Type I diabetes mellitus

It is commonly diagnosed in children and adolescents, but it can occur in adults as well. It is an autoimmune disorder in which the body's own immune system attacks the beta cells in the islets of Langerhans of the pancreas, destroying them or damaging them sufficiently to reduce insulin production (**Gorsuch et al., ١٩٨٣**).The autoimmune attack may be triggered by reaction to an infection for example by one of the viruses as rubella and one of

the Coxsackie virus family***. (Yoon, ١٩٩٠)) and (Szopa et al., ١٩٩٣).***

It is dependant on insulin for metabolic control of the patients' disease. Patients may suffer from more severe form of the disease which is characterized by abrupt onset, increased frequency and severity of ketoacidosis and possibly more severe systemic complications. (***Rees, ٢٠٠٠***).

Formerly, type I diabetes was called "childhood" or "juvenile" diabetes or "insulin dependant" diabetes. Each term is a misnomer, because the obesity in recent years has led to increased incidence of type II diabetes in children and adolescents. So we can not term it as childhood or juvenile diabetes. Furthermore, because insulin is used in treatment of some cases of type II, so insulin dependant diabetes became also a misnomer for type I***. (Kuzuya et al., ٢٠٠٢).***

## Type II diabetes mellitus

Type II diabetes is the most common form of diabetes accounting for ٩٠% to ٩٥% of all cases. (***Newman, ٢٠٠٢***).

It is characterized by "insulin resistance" as body cells don't respond when insulin is present. This is a more complex problem than type I, but usually easier to treat as insulin is still produced. Type II diabetes may go unnoticed for many years as its symptoms are milder and can be sporadic. However, severe

complications can result from unnoticed diabetes, including hypertension, renal failure, and coronary artery disease. ***(O'Keefe et al., ١٩٩٩).***

Type II diabetes may be caused by a number of diseases, such as hemochromatosis, and can be also caused by certain types of medications as long term steroid use. In a lot of cases environmental reasons also play a role. Furthermore, there is a very strong inheritable genetic factor in type II diabetes. **(Atkinson &Maclaren, ١٩٩٠) and (*Yoon, ١٩٩٠*)**.

Type II diabetes was formerly known by many names, including "adult onset diabetes", "obesity-related diabetes" , "insulin-resistant diabetes", or "non-insulin –dependant diabetes"(NIDDM). In addition, there is a group called maturity–onset diabetes of the young (MODY) where diabetes is diagnosed before the age of ٢٥ years, with being non-ketotic and typically responsive to diet. (***Fajans, ١٩٨٩***).

## Type ٣

All other specific forms of diabetes, accounting for up to ٥ % of all diagnosed cases of diabetes, are termed Type ٣:

Type ٣A: genetic defect in beta cells. Type ٣B: genetically related insulin resistance. Type ٣C: caused by hormonal defects. Type ٣D: caused by chemicals or drugs.(***Geneva :WHO ١٩٩٩***).

## Type ٤

Type ٤ or gestational diabetes (any glucose intolerance developed or detected during pregnancy), appears in about ٢-٥ % of all pregnancies. It is temporary and fully treatable, but if untreated it may cause problems. However, about ٢٠-٥٠% of these women go on to develop Type II diabetes. ***(Sherwin, ١٩٩٦).***

## ***Experimental induction of diabetes***

Various surgical, chemical, viral and hormonal methods have been used to induce diabetes in animals. For over ٥٠ years, alloxan was known to produce selective destruction of B-cells in islets of Langerhans (***Klebanoff & Greenbaum, ١٩٥٤***).

***Boquist (١٩٨٠)*** believed that alloxan sensitivity is associated with high inorganic phosphate and low PH. He found that the altered localization and concentration of phosphate cause mitochondrial lesion and finally B-cell necrosis because of absent mitochondrial function.

According to ***Malaisse et al., (١٩٨٢***), alloxan inhibit both glucose oxidation and glucose stimulated insulin release in pancreatic islets. The selective toxicity of alloxan to pancreatic B-cells is attributable to the conjunction of two features: a rapid

cellular uptake of the drug and sensitivity of the B-cell to peroxide.

Alloxan acts as exogenous free radical generator in pancreatic islets (***Asayama et al., ١٩٨٤).*** Furthermore, ***Takasu et al., ١٩٩١*** demonstrated that alloxan stimulate $H^{٢}O^{٢}$ generation, which induce DNA strand breaks in pancreatic islets.

Injection of a single dose of alloxan intrapretonial for three days, then after the last injection, hyperglycemia was confirmed. (***Julio et al., ٢٠٠٠***). However, Production of severe insulinopenic type I diabetes can be obtained by chemical methods, mostly involving; intrapretonial injection of streptozotocin dissolved in citrate buffer (***Thomsen et al., ٢٠٠٢)***.

## ***PATHOPHYSIOLOGY OF DIABETES MELLITUS:***

Many risk factors have been implicated in the pathogenesis of NIDDM such as genetic factors, where if both parents are diabetics the risk of the offspring is at least ٥٠%. In some subtypes of NIDDM, mutations in single genes have been implicated. Mutation may be in the insulin receptor gene or in the post receptor signaling pathway for insulin. (***Foster, ١٩٩٤***).

Hyperglycemia may result from defect in the ability of B cells to secrete insulin. This defect may be due to decrease in the rate of insulin secretion or reduction of B cell mass, it may

also result from defect in the ability of insulin to inhibit hepatic glucose production and promote glucose utilization **(Insulin resistance)**. (***Zimmet,*** ١٩٩٧).

Also, environmental factors may influence the progression of NIDDM such as reduced physical activity, high caloric diet, stresses and drugs. ***(Balkau et al.,*** ١٩٩٧**).**

Finally, obesity is a major risk factor for NIDDM, as the critical link is being insulin resistance**.** ***(Wroblewski et al.,*** ١٩٩٨**).**

## ***Complications of diabetes :***

In diabetic patient, accelerated atherosclerosis involving the coronary, cerebrovascular and peripheral vessels occurs at an early age and with greater frequency. So they are prone to coronary artery diseases. An increased prevalence of lipid abnormalities contributes to accelerated atherosclerosis. Characteristically, triglycerides-rich very –low density (VLD) lipoproteins are elevated, where high-density lipoproteins (HDL) are decreased. Moreover, High cholesterol levels had been demonstrated in diabetic with coronary heart disease. The increased hematocrit ratio and blood viscosity observed