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EFFECT OF METFORMIN ON PERIODONTAL STATUS IN TYPE 2 DIABETES PATIENT: A CROSS SECTIONAL ANALYSIS

Dental Science

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ABSTRACT

Aim: To evaluate the effect of Metformin on periodontium in Type 2 Diabetes patients.
Materials and Method: 30 subjects (Type 2 Diabetes) were included in the study. Subjects were divided into Metformin and Non Metformin groups. Fasting blood sugar (FBS) levels and Russell's Periodontal Index (RPI) were assessed. Radiographic assessment was done using OPG to confirm findings of RPI. Measurements were recorded and subjected to statistical analysis.
Results: There was a statistically non-significant difference seen in the mean FBS between the Metformin & Non-Metformin groups ($p>0.05$), the mean being slightly higher for the Non-Metformin group. There was a statistically non-significant difference seen in the mean RPI between the two groups ($p>0.05$), the mean being slightly higher for the Metformin group.
Conclusion: Metformin, though an anti-hyperglycaemic, does not have a significant beneficial effect on human periodontium, within the limitations of the study.

KEYWORDS

Periodontium, Fasting blood sugar, Metformin, Russell's periodontal index.

INTRODUCTION

Diabetes is a group of metabolic disorders characterised by hyperglycaemia (elevated blood sugar). The main types of diabetes are type 1 diabetes, type 2 diabetes and gestational diabetes.

Type 1 diabetes (in the past, referred to as insulin-dependent diabetes, or juvenile diabetes) describes a condition in which there is a failure to produce insulin as a result of autoimmune destruction of the insulin-producing β-cells in the pancreas.

Type 2 diabetes (previously referred to as non-insulin-dependent diabetes, or adult onset diabetes) results from insulin resistance; that is, there is reduced responsiveness of the cells in the body to insulin, leading to a reduced capacity to transfer glucose out of the circulation and into cells. This leads to hyperglycaemia (elevated blood glucose levels).

The prevalence of type 2 diabetes mellitus (DM) is increasing rapidly worldwide, with a prediction of more than 380 million people to be affected by 2025.¬¬¬

Inflammatory periodontal diseases are the most common chronic inflammatory conditions of man, affecting (if including gingivitis as well as periodontitis) up to 90% of the world's population. When considering severe periodontitis (which typically refers to the presence of pocketing ≥6 mm), the prevalence is generally estimated to be around 5-15% of adults globally.

Periodontitis and diabetes are both highly prevalent conditions, and the association between these two common diseases has been recognised by dental professionals for many years.Epidemiological studies have clearly identified that diabetes is a major risk factor for periodontitis, increasing the risk approximately three-fold compared to non-diabetic individuals, particularly if glycaemic control is poor.

Diabetes has been classically associated with a group of microvascular and macrovascular complications. The microvascular complications include retinopathy (blindness), nephropathy (renal failure), and neuropathy (sensory).

Macrovascular diseases include autonomic, peripheral vascular disease, cardiovascular disease, cerebrovascular disease (stroke) and altered wound healing.

The increased prevalence and severity of diabetes,especially those with poor glycaemic control, led to the designation of periodontal disease as the "sixth complication of diabetes." In addition to the five "classic" complications of diabetes (Retinopathy,Nephropathy ,Neuropathy, Macrovascular disease, Altered wound healing), the American Diabetes Association has officially recognized that periodontal disease is common in patients with diabetes, and the Association's Standards of Care include taking a history of current or past dental infections as part of the physician's examination.

"Flowchart 1 about here"

The primary goal of type 2 DM treatment is to achieve and maintain good glycemic control, and to reduce the mortality and risk of microvascular and macrovascular complications. The current consensus algorithms for medical management of type 2 DM recommend a combination of lifestyle intervention and metformin as initial therapy.

"Flowchart 2 about here"

Metformin reduces blood glucose levels by inhibiting hepatic glucose production and reducing insulin resistance, particularly in liver and skeletal muscle. The plasma insulin levels are unchanged or reduced. Metformin decreases intestinal absorption of glucose, and increases insulin sensitivity by enhanced glucose uptake and utilization in peripheral tissues.

Oxidative stress and inflammation resulting tissue damage are hallmarks of chronic diseases like diabetes. Increased production and/or in effective scavenging of reactive oxygen species (ROS), advanced oxidation protein product(AOPP) and accumulation of advanced glycation end products(AGE)play crucial role in diabetes pathogenesis.

When the oxidant-antioxidant balance is disturbed in favour of ROS, oxidative stress occurs, which is damaging to tissues. A higher amount of ROS release in peripheral blood neutrophils has been reported in periodontitis compared to the healthy subjects. Latest data also reveal reduced antioxidant capacity and increased oxidative stress bioma rkers in periodontitis.

Hyperlipidemia and periodontitis have also been shown to be correlated. Furthermore, a higher ROS and O_2 production have been reported in patients with hyperlipidemia. Increase in ROS and particularly O_2 production play a very important role in the complications arising in diabetes patients.

Metformin reduces intracellular reactive oxygen species levels by upregulating antioxidant thioredoxin via the AMPK-FOX O_3

pathway.

Metformin therapy reduced the ROS formation suggesting diminis hing effect of oxidative stress.

In the light of these findings, considering the relations between periodontal destruction, reactive oxygen species activity and Metform in's role in reducing ROS in diabetes, we conducted a study to evaluate the effect of Metformin on periodontium of type 2 diabetes patients.

MATERIALS AND METHODS

STUDY DESIGN:

30 chronic periodontitis subjects with Type 2 Diabetes Mellitus were selected from Out Patient Department, Department of Periodontics. Subjects with a history of NIDDM for more than one year and developed after the age of 30 were grouped as Metformin users (n=15) and Non-Metformin users (n=15) based on the usage of Metformin. Fasting blood sugar (FBS) levels and Russell's Periodontal Index (RPI) were assessed.

A questionnaire with parameters including age, oral hygiene habits, questions regarding the individual's diabetes profile, was filled by the subjects. Written, informed, signed consent was obtained from all the participants.

CLINICAL MEASUREMENTS:

A William's graduated periodontal probe was used to measure Russell's Periodontal Index scores for both the groups (Fig 1. & Fig 2). Radiographic assessment of bone level was done using an orthopantomogram. Complete heamogram reports were obtained of the study subjects.

STATISTICAL ANALYSIS:

The results of the study were tabulated. The data obtained was compiled on a MS Office Excel Sheet (v 2010) and subjected to statistical analysis using Statistical package for social sciences (SPSS v 21.0, IBM).

Comparison of Russell's Periodontal Index, FBS between the groups of Metformin users and non Metformin users was done using independent t test.

For all the statistical tests, $p<0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

RESULTS:

Mean values of RPI and FBS between Metformin users and Non-metformin users were compared (Table 1).

" Table 1 about here"

There was a statistically non significant difference seen in the mean RPI index between the groups Metformin users & Non Metformin users ($p>0.05$), the mean being slightly higher for the metformin group.

However there was a statistically highly significant difference seen in the mean FBS between the Metformin users & Non metformin users ($p<0.01$), the mean score being higher for the Non-Metformin group. (159.16)

DISCUSSION:

Epidemiological studies have consistently shown that diabetes is associated with increased risk of periodontitis. The majority of research has focused on type 2 diabetes, although type 1 diabetes appears to have an identical effect on risk for periodontitis. It has been reported that patients with diabetes may present to the dental professional with multiple recurring periodontal abscesses, and although this may sometimes be the case, it is not typical.

The mechanisms that link diabetes and periodontitis are not completely understood, but involve aspects of inflammation, immune functioning, neutrophil activity, and cytokine biology. Both type 1 and type 2 diabetes are associated with elevated levels of systemic markers of inflammation. Diabetes increases inflammation in periodontal tissues, with higher levels of inflammatory mediators such as interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α). Accumulation of reactive oxygen species, oxidative stress, and interactions between advanced glycation end products (AGEs) in the periodontal tissues and their receptor (RAGE, the receptor for advanced glycation end products) all contribute to increased inflammation in the periodontal tissues in people with diabetes.

In the human body considered as a whole, a decrease in hyperglcaemia can be obtained by lowering glucose entry to the system (i.e. glucose absorption and/or gluconeogenesis or glucogenolysis), by increasing glucose removal (i.e; glucose oxidation, metabolism and/or glycogen storage), or by both.

Several studies have shown that metformin affects intestinal glucose absorption; however this effect cannot explain its hypoglycaemic action,and the major effect of the drug is on glucose metabolism. Metformin acts potentially via the insulin receptor and the glucose transporters; metformin increases insulin binding and a direct effect on the glucose-transport system has been demonstrated. However, the effects of metformin on periodontium in type 2 diabetic patients have not been investigated.

It is already established that, hyperglycemia stimulates oxidative stress which can be mediated through three main mechanisms: NAD(P)Hoxidase, xanthine oxidase and electron transport chain. Metformin therapy reduced the ROS formation suggesting diminis hing effect of oxidative stress. Advanced oxidation protein product (AOPP) and pentosidine are two important markers of oxidative stress implicated with the pathogenesis in diabetic complications. Greater reduction of AOPP and pentosidine level from baseline was also achieved in metformin administered patients, elucidating that metformin extends added protection to combat the disease pathogenesis.

Large amounts of pro-oxidants are produced in prolonged inflammatory response, as seen in periodontitis. Nitric oxide is the known bronchodilator and a potent inhibitor of platelet adhesion and aggregation and has got a multifaceted role in periodontitis. NO_2 levels are significantly elevated in periodontitis patients. The increased nitric oxide production could be due to stimulation of inducible nitric oxide synthase (iNOS) by lipopolysaccharide of Gram negative bacteria of periodontal lesion.

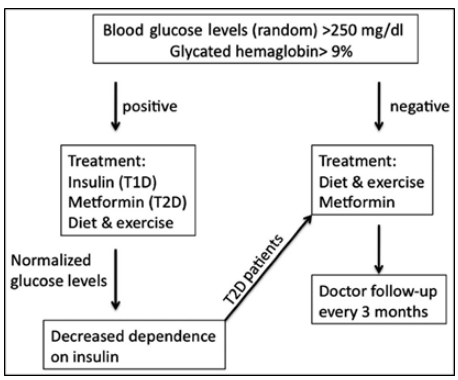
Oxygen is a cofactor for the activity of NOS. In the absence of sufficient oxygen, the functioning of the enzyme NOS becomes affected and consequently, less nitric oxide is produced. Circulation of oxygen in the blood flow is highly impaired in diabetic patients. The diminished level of nitric oxide in diabetic patients was markedly elevated after metformin therapy. Successful antihyperglycemic action of metformin might be recognized as the basis of this phenomenon. Several reports have investigated the effect of Metformin on oxidative stress. Although the actual mechanism is not completely clear as yet.

Thus this is the first study of its kind to evaluate the anti-oxidant effect of the anti-diabetic drug Metformin on periodontium of Type 2 diabetic patients.

CONCLUSION:

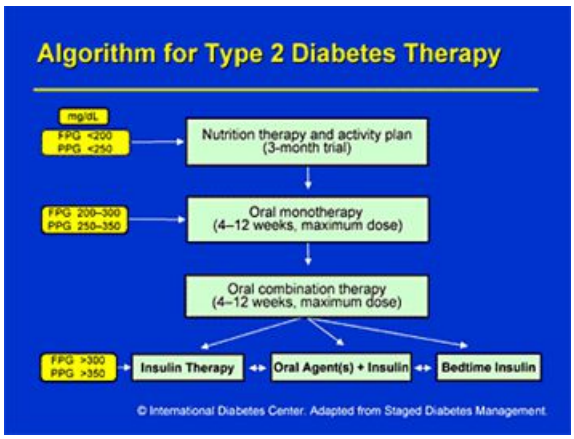
The present study revealed that Metformin, though having an anti-hyperglycaemic effect, does not show a significant beneficial effect on human periodontium, within the limitations of the study.

Flowchart 1.



Flowchart showing treatment for Diabetes

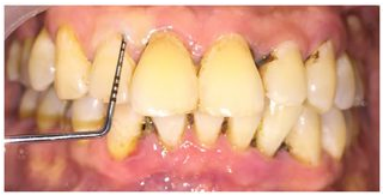
Flowchart 2



Flowchart showing treatment of Type 2 Diabetes mellitus

Figure 1.

a



b

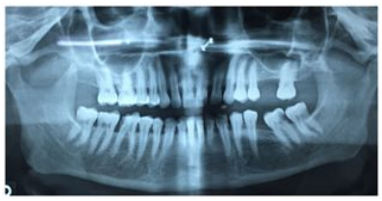
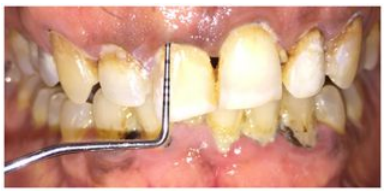
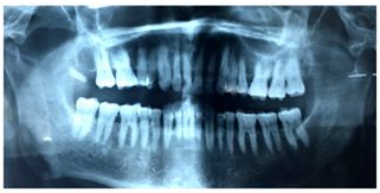


Figure 2.

a



b



Group 2: Non-Metformin users

a. Clinical assessment using William's graduated periodontal probe.
b. Radiographic assessment (OPG)

Table 1.

Table 1.	Groups	N	Mean	Std. Deviation	Std. Error Mean	p value of independent t test
RPI index	Metformin	15	2.74	.998	.258	0.170#
	Non met	15	2.12	1.389	.359	
FBS	Metformin	15	159.16	53.553	13.827	
	Non met	15	111.88	26.104	6.740	0.005**

** = Statistically highly significant difference ($p<0.01$)
# = statistically non-significant difference ($p>0.05$)

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