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ORIGINAL ARTICLE

Relationship between Glycaemic Control and Oral Immunologic Proteins

Relation Entre le Contrôle Glycémique et les Protéines Immunologiques Orales

[1]*O. A. Olayanju, [2]I. N. Mba, [3]O. O. Akinmola, [4]N. E. Awah, [5]E. Ofagbor, [6]O. Okonkwo, [1]O. E. Olasehinde, [1]M. John-Okah, [1]F. Abbiyesuku

ABSTRACT

BACKGROUND: Attaining a good glycaemic control is usually the target for therapy in diabetic patients as this is expected to prevent both acute and chronic complications. Oral infections are however very common among diabetic patients despite the presence of many immunologic proteins in the saliva. This study was designed to determine the impact of glycaemic control on levels of these proteins in diabetic patients.

METHODS: Salivary lysozyme, histatins, immunoglobulin A and immunoglobulin G were measured in diabetic patients. The levels of these immunologic proteins were compared between patients whose HbA_{1c} were less than 7% and those whose values were greater than or equal to 7%.

RESULTS: A total of 95 participants were recruited for this study with 37 (38.9%) of them having a median HbA_{1c} of 6.3% (IQR 5.3- 6.6) and the remaining 58 (61.1%) having a median HbA_{1c} of 9.1% (IQR 8.1–10.5). There was no significant difference in salivary lysozyme (31.24 vs 33.77 ng/ml; p = 0.69), histatins (9.65 vs 9.17 ng/ml; p = 0.27), IgA (12.79 vs 12.19 µg/ml; p = 0.16) and IgG (31.29 vs 32.49 µg/ml; p = 0.85) between the group with good and those with poor glycaemic control.

CONCLUSION: This study showed that glycaemic control does not impact the levels of salivary immunologic proteins in diabetic patients, so quality attention should be given to oral care to avoid the development of oral complications. **WAJM 2022; 39(10): 1062–1067.**

Keywords: Diabetes, Glycaemic control, Salivary proteins, Oral cavity, Immunologic proteins.

RÉSUMÉ

CONTEXTE: L'obtention d'un bon contrôle glycémique est généralement l'objectif du traitement des patients diabétiques, car il est censé prévenir les complications aiguës et chroniques. Les infections buccales sont cependant très fréquentes chez les patients diabétiques malgré la présence de nombreuses protéines immunologiques dans la salive. Cette étude a été conçue pour déterminer l'impact du contrôle glycémique sur les niveaux de ces protéines chez les patients diabétiques.

MÉTHODES: Le lysozyme, les histatines, l'immunoglobuline A et l'immunoglobuline G salivaires ont été mesurés chez les patients diabétiques. Les niveaux de ces protéines immunologiques ont été comparés entre les patients dont le HbA1c était inférieur à 7 % et ceux dont les valeurs étaient supérieures ou égales à 7 %.

RÉSULTATS: Au total, 95 participants ont été recrutés pour cette étude, 37 (38,9 %) d'entre eux ayant une HbA1c médiane de 6,3 % (IQR 5,3- 6,6) et les 58 autres (61,1 %) ayant une HbA1c médiane de 9,1 % (IQR 8,1- 10,5). Il n'y avait pas de différence significative dans le lysozyme salivaire (31,24 vs 33,77 ng/ml ; p= 0,69), les histatines (9,65 vs 9,17 ng/ml ; p= 0,27), les IgA (12,79 vs 12,19 ?g/ml ; p= 0,16) et les IgG (31,29 vs 32,49 ?g/ml ; p= 0,85) entre le groupe avec un bon et celui avec un mauvais contrôle glycémique.

CONCLUSION: Cette étude a montré que le contrôle glycémique n'a pas d'impact sur les niveaux de protéines immunologiques salivaires chez les patients diabétiques, une attention de qualité devrait donc être accordée aux soins bucco-dentaires pour éviter le développement de complications orales. **WAJM 2022; 39(10): 1062–1067.**

Mots clés: Diabète, Contrôle glycémique, Protéines salivaires, Cavité orale, Protéines immunologiques.

[1]Department of Chemical Pathology, Ben Carson Snr College of Health and Medical Science, Babcock University, Ilisan, Nigeria. [2]Department of Chemical Pathology, Nile University of Nigeria, Abuja, Nigeria. [3]Department of Chemical Pathology, Lagos University Teaching Hospital, Lagos, Nigeria. [4]Department of Chemical Pathology, University College Hospital, Ibadan, Oyo State, Nigeria. [5]Royal Free London, NHS Foundation Trust, London, England. [6]Department of Anatomical Pathology, University College Hospital, Ibadan, Oyo State, Nigeria.

***Correspondence:* Dr. Olatunde Olayanju,** Department of Chemical Pathology, Ben Carson Snr College of Health and Medical Science, Babcock University, Ilisan, Nigeria. Email: olayanjuo@babcock.edu.ng

INTRODUCTION

The global prevalence of diabetes mellitus has continued to increase over the years and recent projections for the next two decades do not suggest any hope for a reprieval. Currently placed at 10.5% amongst patients aged 20 to 79 years, the prevalence of diabetes is estimated to rise to 12.2% by the year 2045 according to the international diabetes federation.[1] Increase in sedentary lifestyle, unhealthy diet, cigarette smoking and weight disorders are some of the factors associated with this increase and they cut across most continents of the world.[2] These modifiable factors continue to undermine innovative strides in drug development and other potential modalities targeted at glycaemic control including the discovery of insulin inhibitory receptor-inceptor and portable artificial pancreas.[3,4] In a reactionary move to stem this tide, the World Health Organisation (WHO) launched the global diabetes impact in 2021 with the primary aim of increasing awareness about diabetes, ensuring patients have quality care and reducing risks associated with diabetes.[5] However, diabetes and its complications continue to contribute to increasing number of hospital attendance and inpatient admission in many cases.

Life threatening diabetes complications can result in emergencies requiring resuscitative measures in intensive care units. Hyperglycaemic hyperosmolar state and diabetic ketoacidosis are acute clinical complications usually necessitating prompt interventions to salvage patients' lives.[6] Other acute complications like lactic acidosis and electrolyte derangement with their consequent disabilities are also common occurrences in clinical practice.[7] Chronic complications of diabetes, usually occurring in patients with long standing disease, especially in those with poor glycaemic control are well documented. The macrovascular types, essentially the cardiovascular diseases, are major causes of mortality globally while the microvascular types, namely retinopathy, neuropathy and nephropathy contribute to most hospital admissions and are linked with poor treatment outcomes.[8,9] Furthermore, chronic hyperglycaemia is associated with development of oral infections which also plays a very important role in glycaemic control and quality of life in affected patients and this deserves significant consideration.[10]

Apart from oral candidiasis which is widely reported in diabetic patients, several other inflammatory, autoimmune and bacterial infections occur more commonly in the oral cavity of diabetic patients than in the general population.[11–13] Modulation of immune cells by advanced glycation end products, decreased phagocytosis and chemotaxis by polymorphonuclear cells, and dysfunctional humoral immunity are some of the major explanations put forward for increased susceptibility of diabetic patients to these oral infections.[14,15] This position is evenly shared between type 1 and type 2 diabetes suggesting that this classification produces no preference, the chronic hyperglycaemia being the common basis for the increased susceptibility.[16,17] Thus, it is reasonably logical to hypothesize that stabilizing plasma glucose level at therapeutic target range will reduce the chances of developing infections. This impression is justified by several reports in which good glycaemic control conferred significant advantage on patients under study for the presence or the development of infection in various research settings.[18–20]

However, in the oral cavity which is predisposed to a wide range of infections as a result of hyperglycaemia, it is not clear how glycaemic control impact the quantity and the functionality of immunologic proteins in the saliva. Several hundreds of immunologic proteins have been isolated in saliva and they belong to either the adaptive or the innate immune system in the body, depending on their mode of synthesis and mechanism of action.[21,22] Prominent among the innate oral immunologic proteins are lysozyme and histatins. Salivary lysozyme is a potent anti-inflammatory and antibacterial protein and it serves as the first line of protection against microbial agents in the oral cavity, which it does by breaking down the cell wall of the invading organisms.[23] Fungal infections on the other hand are kept in check by the salivary histatins due to its potent broad antifungal spectrum.[24] The adaptive immunological response in the saliva is usually executed by the immunoglobulins, which are either secreted locally by the salivary glands or derived from the serum immunoglobulin leakages.[25] All these immunologic proteins maintain the required stability in the oral cavity in healthy individuals but become compromised in chronic hyperglycaemic state, thereby predisposing to oral infections. The objective of this study is to determine whether achieving good glycaemic control in diabetic patients can improve the levels of these immunologic proteins.

METHODS

Study design and setting: This was a cross-sectional study conducted at the chemical pathology department, University College Hospital Ibadan, Nigeria. The study was conducted between May 2019 and August 2019 among patients attending the medical outpatient clinic and the metabolic research ward within the stipulated period.

Ethical approval: Informed consent was obtained from each of the participants and ethical approval for the study was obtained.

Participants and variables: Type 2 diabetic patients above the age of 18 years were randomly selected from the outpatient clinic. A structured questionnaire was administered to each participant at the onset of the study to obtain information regarding their bio-demography and health data. Relevant information obtained included age, gender, weight, height, level of education, duration of diagnosis, medication history, frequency of clinic visitation, co-morbid clinical conditions and self-assessment of general wellbeing. Blood and saliva samples were collected for laboratory analysis. Cigarette smokers and participants on immunosuppressive medications were exempted from the study because they are potential confounders.

Sample collection and processing: About 5 ml of blood was collected from the participants through venepuncture; an aliquot of 2 ml was dispensed into an

EDTA bottle for HbA_{1c} measurement and the remaining into a fluoride oxalate bottle for fasting plasma glucose measurement. Samples for HbA_{1c} were stored in the fridge for a maximum of three days in order to obtain a reasonable number for batch analysis. Analysis was done using High Performance Liquid Chromatography (HPLC) on BIO-RAD D10 platform according to the manufacturer's instructions. The samples for fasting plasma glucose were centrifuged at 3000 radian per minute to obtain the plasma, which was transferred to a plain bottle and stored at –20 degrees until the time of analysis. Analysis was done using the Landwind C100 autoanalyser according to the manufacturer's instructions.

Unstimulated saliva sample was collected from each participant by passively drooling into a clean universal bottle after rinsing their mouth with clean water. The samples were transferred into plain test tubes for centrifugation at 3000 radians per minutes for 15 minutes, and the supernatants pipetted into Eppendorf bottles for storage at –20 degrees until the time of analysis. Salivary immunoglobulins A and G, lysozyme and histatins were measured using enzyme linked immunosorbent assay technique according to the manufacturer's instructions (Melsins Medicals, Changchun, China).

Quantitative Variables

The participants were divided into two groups based on their level of glycaemic control. Those who had HbA_{1c} less than 7% were classified as having good glycaemic control while those who had HbA_{1c} greater than or equal to 7% were classified as having poor glycaemic control. Biodemographic data, clinical data and levels of the oral immunologic proteins were compared between the two groups.

Statistical Analysis

Data was subjected to normality test, variables which showed normal distribution were reported as mean ± standard deviation, while the others were reported as median (interquartile range). Differences between participants with good glycaemic control and those with poor glycaemic control were determined using independent samples T and Mann-Whitney U tests as appropriate, depending on nature of data. Logistic regression was done to determine biodemographic and clinical data that were predictive of good glycaemic control. Variables with p values less than 0.1 were used to compute a multivariate model for factors predictive of achieving a good glycaemic control. Correlation analysis was also done to determine the relationship between oral immunologic proteins and fasting plasma glucose, HbA_{1c} and duration of treatment for diabetes. P values less than 0.05 were considered significant, and data was analysed using Statistical Package for Social Sciences (SPSS) version 26 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 95 diabetic participants were recruited for this study. Thirty-seven (38.9%) of them had a good glycaemic control, with a median HbA_{1c} of 6.3% (IQR 5.3–6.6) while the remaining fifty-eight (61.1%) had a poor glycaemic control with a median HbA_{1c} of 9.1% (IQR 8.1–10.5). There was no significant difference between the height (p = 0.65), weight (p = 0.84), and BMI (p = 0.57) of the two groups. However, the group with good glycaemic control was younger (p = 0.005) and had been on treatment for a shorter duration (p = 0.02) compared to the group with poor glycaemic control. There was no significant difference in levels of salivary lysozyme (p= 0.69), salivary histatins (p= 0.27), salivary IgA (p= 0.16) and salivary IgG (p= 0.85) between the group with good and those with poor glycaemic control (Table 1).

Univariate logistic regression analysis showed that a lower fasting plasma glucose (O.R. 0.984; p=0.04), younger age (O.R. 0.957; p=0.009), regular clinic visit (O.R. 2.786; p=0.08), a lower BMI (O.R. 0.113; p=0.001), and early phase of treatment commencement (O.R. 0.931; p=0.04) were independent predictors of achieving a good glycaemic control. Adjusted odd ratio suggested that participants with BMI lower than 30 kg/m^2 (O.R. 0.038; p= 0.001) and those with reduced fasting plasma glucose (O.R. 0.974; p= 0.02) are more likely to achieve a good glycaemic control (Tables 2 and 3). Different degrees of correlations were established between the levels of the oral immunologic proteins and fasting plasma glucose, HbA_{1c} and duration of treatment for diabetes but none of them were statistically significant (Table 4).

DISCUSSION

The oral cavity is replete with immunologic proteins which protect it against disease causing microorganisms. However, the development of oral infections is a common occurrence in diabetic patients, and this has implications for their treatment outcomes and quality of life. Diabetes has been

Table 1: Comparison of Demographics and Clinical Data between Diabetic Participants with good Glycaemic Control (HbA_{1c} <7%) and those with Poor Glycaemic Control (HbA_{1c}≥7%)

Variables	Good Control (n=37)	Poor Control (n=58)	p-value
Age (years)	54.1 ± 12.3	61.9 ± 13.9	0.05
Height (m)	1.60 (1.54–1.65)	1.57 (1.54–1.65)	0.65
Weight (kg)	71.5 (63.8–84)	75.5 (63–82.4)	0.84
BMI (kg/m^2)	28.3 (24.5–32.7)	29.3 (24.6–33.5)	0.57
Treatment duration (years)	7 (3–10)	9.5 (5–17)	0.02
HbA_{1c} (%)	6.3 (5.3–6.6)	9.1 (8.1–10.5)	<0.001
FPG (mmol/ L)	5.8 (5.0–6.8)	6.5 (5.2–8.6)	0.07
Salivary Histatins (ng/ml)	9.65 (8.43–10.52)	9.17 (7.27–10.20)	0.27
Salivary Lysozyme (ng/ml)	31.24 (25.6l2–40.41)	33.77 (25.72–40.19)	0.69
Salivary IgG (µg/ml)	31.29 (25.68–37.75)	32.49 (24.93–38.83)	0.85
Salivary IgA (µg/ml)	12.79 (12.18–13.61)	12.19 (10.28–13.77)	0.16

BMI, Body Mass Index; FPG, Fasting Plasma Glucose; HbA_{1c}, Glycated Haemoglobin A_{1c}.

Table 2: Univariate Logistic Regression for achieving Good Glycaemic Control

Variables	Odds Ratio (95% C.I)	p-value
Age (years)	0.957 (0.927–0.989)	0.009
Weight (kg)	0.992 (0.964–1.021)	0.59
Height (m)	2.976 (0.006–1559.6)	0.73
BMI>30 (kg/m^2)	0.113 (0.032–0.402)	0.001
FPG (mmol/ L)	0.984 (0.970–0.999)	0.04
Gender (M)	0.681 (0.285–1.630)	0.39
Lysozyme (ng/ml)	0.993 (0.954–1.033)	0.71
Histatins (ng/ml)	1.048 (0.906–1.211)	0.53
IgA (µg/ml)	1.087 (0.958–1.232)	0.19
IgG (µg/ml)	1.008 (0.975–1.041)	0.64
Duration of diabetes (years)	0.931 (0.870–0.996)	0.04
Clinic visit	2.786 (0.899–8.627)	0.08
SMBG	1.324 (0.469–3.738)	0.59
Comorbid diseases	0.691 (0.296–1.610)	0.39
Tertiary education	0.954 (0.795–1.122)	0.52

BMI, Body Mass Index; FPG, Fasting Plasma Glucose; IgA, Immunoglobulin A; IgG, Immunoglobulin G; SMBG, Self Monitoring of Blood Glucose.

Table 3: Multivariate Logistic Regression for achieving Good Glycaemic Control

Variables	Odds Ratio (95% C.I)	p-value
Age (years)	0.978 (0.930–1.028)	0.39
FPG (mmol/ L)	0.974 (0.953–0.995)	0.02
BMI> 30 (kg/m^2)	0.038 (0.006–0.267)	0.001
Duration of diabetes (years)	0.990 (0.899–1.091)	0.85
Clinic visit	59.58 (0.649–5466.9)	0.08

BMI, Body Mass Index; FPG, Fasting plasma glucose; IgA, Immunoglobulin A.

Table 4: Table of Correlations between Salivary Immunologic Proteins and Treatment Duration, HbA_{1c} and Fasting Plasma Glucose

Variables	Spearman's Correlation	p-value
Correlation between Salivary Proteins and Treatment Duration		
Salivary Lysozyme (ng/ml)	–0.017	0.88
Salivary Histatins (ng/ml)	–0.118	0.29
Salivary IgA (µg/ml)	0.006	0.99
Salivary IgG (µg/ml)	0.068	0.54
Correlation between Salivary Proteins and HbA_{1c}		
Salivary Lysozyme (ng/ml)	0.045	0.67
Salivary Histatins (ng/ml)	–0.132	0.21
Salivary IgA (µg/ml)	0.145	0.16
Salivary IgG (µg/ml)	–0.02	0.85
Correlation between Salivary Proteins and FPG		
Salivary Lysozyme (ng/ml)	–0.110	0.37
Salivary Histatins (ng/ml)	0.015	0.91
Salivary IgA (µg/ml)	–0.099	0.35
Salivary IgG (µg/ml)	0.068	0.52

IgA, Immunoglobulin A; IgG, Immunoglobulin G; HbA_{1c}, Glycated haemoglobin; FPG, Fasting Plasma Glucose.

shown to compromise immunologic responses by altering the functionality of both the innate and adaptive immune apparatuses, hence the high prevalence of oral infections. A good glycaemic control is highly desirable among patients undergoing treatment, but it is not clear if this impacts positively on the oral immunologic proteins. This study found no difference in the level of oral immunologic proteins between diabetic participants with good and those with poor glycaemic control, and no significant correlation between the salivary immunologic proteins and glycaemic control. It also found that low fasting plasma glucose, BMI less than 30 kg/ m^2 and regular attendance in clinic were predictors of good glycaemic control.

A good glycaemic control is undoubtably the main target of diabetes treatment, and it has been associated with improved oral health and reduced prevalence of oral disorders like periodontitis.[26,27] Thus, it was envisaged that patients who can achieve HbA_{1c} less than 7% will have significantly higher values of oral immunologic proteins. On the contrary, this study negated the assertion suggesting that once diabetes is established in an individual, the overall humoral immunity of the oral cavity becomes compromised without recourse to glycaemic control. This was the same position reported in a Nigerian study where a group of 150 type 2 diabetes patients showed no significant impact of a good glycaemic control on the values of immunoglobulin A and immunoglobulin M.[28]

The practical implication of this finding was demonstrated in a German study investigating the impact of glycaemic control on the diversity and composition of oral microbiota in type 2 diabetic patients. It was shown that glycaemic control did not show significant impact on oral microbial ecology of the patients, unlike obesity which showed otherwise in the same study.[29] In other studies evaluating the role of glycaemic control on the post-extraction epithelialisation and development of post-procedure complications in a group of diabetic patients, again, there was no difference in the rate of healing between diabetic

patients whose HbA_{1c} were above and those below 7%.[30,31] It is pertinent to state that these were not the only perspectives, as several other studies showed, on the contrary, that glycaemic control is prerequisite to achieving a healthy oral cavity and alleviate the risk of oral infection.[32–34]

The ultimate goals for diabetes therapy are to alleviate symptoms, reduce long-term complications and improve quality of life.[35] HbA_{1c} is a marker of long-term glycaemic control, and the knowledge of patient-related factors for attaining a good glycaemic control could guide physicians to better manage diabetic patients. This study showed that regular clinic visit, reducing fasting plasma glucose (FPG), and BMI < 30 kg/ m^2 were important predictors of good glycaemic control. The effect of FPG on glycaemic control as shown in this study is corroborated by other studies done much earlier.[36,37] However, in another study where both FPG and postprandial plasma glucose (PPG) were measured, PPG was shown to better correlate with glycaemic control in diabetic patients.[38,39] The reasons in favour of PPG as a better correlate of glycaemic control was that patients are mostly in the postprandial state for the most part of the day. Hence, PPG was recommended as a measure of glycaemic control in places where measurement of glycated haemoglobin is not possible.[36,40]

Obesity is a major factor in the pathogenesis of Type 2 DM, and weight reduction is a major therapeutic goal for a successful treatment. Monitoring of BMI forms an important component of care in metabolic clinics, and it can be used to measure treatment success in Type 2 diabetic patients. In this study, it is not surprising to find that BMI less than 30 kg/ m^2 was associated with good glycaemic control and this has been similarly reported in the literatures.[41–43] Regular clinic visit was another important factor that predicts good glycaemic control in this study. This is supported by studies that showed that patients who attended clinic for up to four times within a year had better glycaemic control, and reduced risk for developing cardio-vascular complications.[44,45] To further emphasize the role of clinic visits, studies that compared the favourable outcome rate between patients in group medical appointments and those with individual appointments found that patients who attend clinic in groups with other diabetic patients had better glycaemic control in the long run.[46,47]

There are limitations to this study. Over 300 proteins have been isolated from the saliva but most of them are present in very low concentrations and have no role in immunologic defence of the oral cavity. The four immunologic proteins selected for this study are those that play a significant role in protecting the oral cavity against microbial agents.[21] A study with a larger number of participants is strongly advocated to consolidate the findings of this study.

In conclusion, this study did not support the hypothesis that achieving a good glycaemic control will improve the levels of oral immunologic proteins, suggesting that the susceptibility to oral infections in diabetic patients may be irreversible. Thus, the physicians and the patients should be intentionally proactive in maintaining a good oral hygiene in order to forestall the development of oral infections in diabetic patients.

Conflict of Interest

Authors have none to declare.

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