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Clinical Oral Findings and Salivary Analysis of Patients with and Without Diabetes Mellitus

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Keywords

Diabetes mellitus; Salivary flow rate; Salivary glucose

Abstract

Aims: To compare clinical oral findings and salivary changes in diabetic and non-diabetic patients.

Material and methods: This comparative cross-sectional study was conducted at the Endocrinology Clinic of Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile Ife (Cases), the controls were volunteers among staffs and students of the hospital community. Participants were interviewed and examined. Saliva was collected using spitting method and salivary flow rate was determined using volumetric method. Salivary PH, Urea, Creatinine and glucose concentration was determined using Randox BT29 4QY kit.

Results: Total of 100 diabetics and 100 non-diabetics, mean age 54.81+12.23 yr, participated. History of toothache and gum bleeding was significantly more frequent among diabetic subjects, p=0.001 and 0.001 respectively. Salivary flow rate is significantly lower among diabetics 0.32+0.13 ml/min), flow rate was also lower among female. Salivary glucose, urea and creatinine were significantly higher among diabetics while their urine is more acidic. Older age group showed higher concentration of salivary glucose, urea, creatinine, and reduced pH than in younger population. Data analysis was done using STATA 13 statistical software. Wilcoxon rank-sum test was used to compare continuous variables between diabetics and non diabetes

Conclusion: Oral problems and saliva alterations are significantly higher among diabetics especially among male participants of older age groups.

Clinical significance: The significant association between prevalence of oral lesions among diabetes as well as significant qualitative changes in saliva of diabetes is a potential noninvasive tool of monitoring diabetes and could enhance the multidisciplinary management approach in its management.

Introduction

The use of saliva as a diagnostic tool has grown to become very popular in the management of systemic diseases. Changes in saliva composition often reflects the general state of health especially in some disease conditions such as diabetes mellitus [1], HIV/AIDS [2], Renal diseases and psychological stress [3,4]. In additions to underlying systemic diseases, salivary production is also affected by age and sex of the patients.

Salivary secretion occurs in two stages; first is the primary secretion by acini cells. At this first stage, the acini cells of salivary gland secrete the primary saliva from the substrate made available through the plasma. This first formed saliva is essentially an ultra-filtrate of the plasma and is called primary saliva [5]. The second step is the modification of the primary saliva as it flows down the duct; this is done by the ductal epithetical cells. This result is the formation of secondary saliva which will eventually be secreted into the mouth [6]. Second is the modification process which comprises secretion and selective reabsorption of substances into and from the plasma respectively. Due to the presence of similar anchor protein called claudin 16 at the epithelia tight junctions of salivary glands, renal tubules and breast; the mode of action of salivary ductal epithelia cells has been likened to that of respective cells in urine (renal tubules) and breast milk production [7]. The modification process on the saliva at this secondary stage is largely dependent upon the present plasma concentrations of the respective metabolites. The implication is that the higher the concentration of markers of systemic problems in the blood, the higher will be the concentration in the saliva and this is a good rationale for using saliva as a non-invasive replacement for plasma in diagnosis. A good example is the blood sugar, when the blood sugar is high as it happens in DM patients; it implies a corresponding increase in the salivary glucose. The same will also be applicable to some other substances in the blood such as urea, creatinine, antibody concentration, hormones and drugs.

The average unstimulated salivary flow rate of healthy adult ranges from 0.1-0.5 ml/min while the stimulated flow rate was found to be higher, 1-2 ml/min. Studies had shown that patients with diabetes mellitus have lower flow rates [8-10]. Glucose is not a constituent of saliva in a healthy individual.

The pH of saliva of patients with oral lesions has been shown to be at variants with apparently healthy patients [11]. Diabetic patients had acidic saliva compared to non-diabetic patients. Salivary urea and creatinine also differs in diabetic and non-diabetic patients [8,12].

The prevalence of DM is on the increase daily probably as a result of changing to westernized diet as well as sedentary lifestyle. Diabetes is also associated with complications such as CVS, renal failures, amputation, infection and oral problems [13]. It therefore leads to reduce quality of life and the burden on the community at large is quite enormous. Early diagnosis and management of this condition is therefore important and all hands must be on desk to achieve

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this all important goal. The routine/conventional test is the use of plasma sugar which may be painful and require more skills when compared with saliva collection. Saliva is a potential alternative fluid for screening, diagnosis and monitoring the patients. Several studies have been conducted to look into salivary parameters in diseased condition but many did not relate the salivary findings to the severity of the oral symptoms and saliva parameters. The present study is designed to determine salivary physical and chemical constituents in diabetes and non-diabetes individuals, relating the findings with the severity of oral signs and symptoms.

Materials and Methods

This study was designed as a comparative cross-sectional study comparing the clinical features and salivary analysis of diabetic and non-diabetic patients who presented at Obafemi Awolowo University, Ile Ife from January, 2019 to June, 2019. Two groups of subjects were selected: Group a (Diabetic patients) were selected from the pool of patients who presented at Endocrinology clinic for treatment. Group B were apparently healthy and non-diabetic volunteers among staff and students of Obafemi Awolowo University, Ile Ife. Group B subjects were subjected to urinalysis screening test using Combic 9 urinalysis kit, only those with negative test were recruited. The subjects were selected using simple random method.

Ethical approval

Ethical approval was sought and obtained from the Research and Ethics Committee of the institute of Public Health Obafemi Awolowo University. Each participant was well informed and gave their consent before undertaking the study on voluntary basis. Participants were also free to decline from participating in the study at any time during the study period. Information obtained from the participants was treated with utmost confidentiality.

Sample size calculation

Salivary flow rate was used to calculate the sample size since variation in salivary flow is a common finding in many cases of systemic illness. Sample size was calculated using he formulae as applicable to studies comparing two means as reported by Eng (2003) [14].

$$N=\frac{4\delta^2(Z_{crir}+Z_{pwr})2}{D2}$$

Where, N is the total number of samples requires for the two groups Zcrit is a constant value of 1.96 at a clinical significance of 0.05. Zpwr, also a constant which equals 1.645 at a statistical power of 0.95. The symbol ð is the assumed SD of each group. Oyetola et al. had reported the mean salivary flow rate as 0.398 SD 0.25 mL/min [15], therefore SD will be taken as 0.25. D is the total width of an expected Confidence Interval (CI) and was set at 1.3. With the power of 90% and the significance level of 0.05, a sample size of 180 subjects was obtained and rounded up to 200 to allow for attrition

$$N=\frac{4\times2.5^2\times(1.96+1.645)^2}{1.3^2}$$

N= 180

To allow for attrition, N=200. Each group will therefore require 100 participants.

Data collection

The tool used for the data collection was questionnaire. Section A collected information on the participants' biodata such as age, sex, tribe, occupation and so on. Section B has information on oral and general symptoms of diabetes. Section C contains the salivary and blood findings.

Saliva collection

Spitting method, as reported by Srivastava et al. 2018 was used to collect saliva for this study [16]. Samples were collected between 10hrs and 12 hrs to minimize the effect of diurnal variation on the quantity and quality of saliva. Participants were asked to avoid food intake one hour before the procedure. Subjects were given saliva jar and were asked to spit into the jar for five minutes. Saliva collection time was determined using a stop watch. Salivary flow rate was calculated by dividing the total volume collected by a factor of 5 to get the flow rate in ml/min. Thereafter, the saliva was transported to the laboratory immediately for analysis.

Laboratory procedures

Estimation of salivary urea: RandoxKits BT29 4QY, United Kingdom was used to estimate salivary urea. The kits followed Urease- Berthelot method of urea estimation. The ammonia is the measured photometrically by Berthelot's reaction. The procedure for the measurement is essential as contained in the manufacturer instructions and the salivary concentration of urea was calculated using the formula:

$$\frac{\text{Absorbance of the sample (saliva)} \times \text{Standard Concentration}}{\text{Saliva=Absorbance of standard}}$$

Standard concentration is a constant =13.10 mmol/L

Estimation of salivary creatinine

This was done using RandoxKits BT29 4QY ®, United Kingdom. The kits operate on the principle that creatinine in alkaline solution reacts with picric acid to form a colored complex. The procedure for the measurement is essential as contained in the manufacturer instructions.

The salivary concentration of creatinine was calculated using the formula:

$$\frac{\text{Absorbance of the sample (saliva)} \times \text{Standard Concentration}}{\text{Saliva=Absorbance of standard}}$$

Standard concentration is a constant =169 µmol/L

Estimation of salivary glucose

This was done using RandoxKits BT29 4QY, United Kingdom The kits followed Urease- Berthelot method of urea estimation. The procedure for the measurement is essential as contained in the manufacturer instructions.

The salivary concentration of glucose was calculated using the formula:

$$\frac{\text{Absorbance of the sample (saliva)} \times \text{Standard Concentration}}{\text{Saliva=Absorbance of standard}}$$

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Table 1: Sociodemographic of the Participants.

Characteristics	Subjects with Diabetes	Subjects without Diabetes	All Subjects	P value
Sex Male Female **Total (%)**	 32(34.8) 68(63.0) **100**	 60(65.5) 40(37.0) **100**	 92(100) 108(100) **200 (100)**	P=0.0001*
Mean age (SD)	54.13+12.05	55.48+12.4	54.81+12.23	0.2184
Age Category (years) <20(%) 21-30 (%) 31-40(%) 41-50 (%) 51-60 (%) >60 (%) **Total (%)**	 1 (1) 3 (3) 9 (9) 18 (18) 31 (31) 38 (38) **100 (100)**	 0 (0) 3 (3) 10 (10) 29 (29) 29 (29) 29 (29) **100 (100)**	 1 (0.5) 6 (3) 19 (9.5) 47 (23.5) 60 (30) 67 (33.5) **200 (100)**	0.409
Ethnicity Yoruba Ibo Hausa **Total (%)**	 94 (94) 5 (5) 1 (1) **100 (100)**	 97 (97) 3 (97) 0 (0) **100 (100)**	 191 (95.5) 8 (4) 1 (0.5) **200 (100)**	0.498
Occupation Unemployment Civil servants Trading Schooling Retiree **Total (%)**	 6 (6) 27 (27) 44 (44) 2 (2) 2 (2) **100 (100)**	 5 (5) 26 (26) 45 (45) 46 (46) 2 (2) **100 (100)**	 11 (5.5) 53 (26.5) 89 (44.5) 48 (45) 4 (9) **100 (100)**	0.999
Education Status Illiterate Primary Secondary Tertiary Post graduate **Total (%)**	 6 (6) 18 (18) 27 (27) 46 (46) 3 (3) **100 (100)**	 14 (14) 20 (20) 30 (30) 36 (36) 0 (0) **100 (100)**	 20 (10) 38 (19) 57 (28.5) 82 (41) 3 (1.5) **200 (100)**	0.107

Wilcoxon rank-sum test * Statistical significant

Estimation of salivary pH

This was done using pH meter. The instrument was first calibrated by using standard buffer solution of 4.18, 8 and 11.5 respectively and there after 0.0 Lml of the sample (saliva) was carried with a pipette to come in contact with the sensitive part of the probe of the pH meter. The pH of the saliva shows immediately on the screen.

Statistical analysis

Data analysis was done using STATA 13 statistical software (StataCorp, College Station, Texas). Descriptive statistics were used to characterize socio-demographic variables (such as age and sex) and the presence of symptoms. Analyzing for descriptive factors for salivary constituents and age pf participants with continuous variables include checking for mean, median, mode, and range as appropriate. The continuous variable was checked for normality test using Shapiro-Wilks test. Comparison of the mean values of salivary constituents at the dichotomized age groups and sex were done using students-test and Wilcoxon rank-sum test as appropriate. Statistical significance was set at $p<0.05$.

Results

Sociodemographic of the participants

A total of 200 subjects participated in the study, 92 (46%) males and 108 (54%) females. Their mean age + SD was 54+12.23. Majority of the participants were trader with at least primary education. Yoruba ethnicity (95.5%) was the most common tribe. More than three-quarter of the participants were above 40 years old (Table 1).

Oral symptoms and health practices

More than three quarter of the participants had never visited a dentist before, especially those without diabetes (p=0.18). History of tooth ache, spontaneous toothy loss, gum bleeding, taste impairment and mouth odor were significantly higher among diabetes p=0.0001, 0.006, 0.0001, 0.0001, 0.0001 and 0.001 respectively. Most of them brush once daily using tooth brush and toothpaste only (Table 2).

Sex variations in physical and biochemical analysis of salivary constituents of subjects

The mean salivary flow rate is higher in males than females and was significantly lower in diabetes patients, p=0.0077. The saliva of Diabetes subjects was found to be significantly more acidic compare to those without diabetes (p=0.0081). Salivary glucose was higher in female diabetic subjects, the difference was statistically significant, p=0.004. Salivary creatinine and urea was significantly higher in diabetes, p=0.00001 and 0.0001 respectively (Table 3).

Age variations in physical and biochemical analysis of some salivary constituents

Mean salivary flow rate is slightly higher among subjects above 50 years, but the difference was not statistically significant, p=0.226. Older subjects also had more acidic saliva the difference also not

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Table 2: Oral Symptoms and Health Practices.

Characteristics	Participants with Diabetes	Participants without Diabetes	All Subjects	P value
Have you ever visited Dentist for checkup or treatment before?				
Yes	21 (21)	9 (9)	30 (15)	0.018*
No	79 (79)	91 (91)	170 (85)	
History of toothache				
Yes	38 (38)	5 (5)	43 (21.5)	0.0001*
No	62 (62)	95 95)	157(78.5)	
History of spontaneous tooth loss				
Yes	20 (20)	2 (2)	22 (11)	0.006*
No	80 (80)	98 (98)	178 (89)	
History of gum bleeding				
Yes	35 (35)	5 (5)	40 (20)	0.0001*
No	65 (65)	95 95)	160 (80)	
Presence of taste impairment				
Yes	13 (13)	1 (1)	14 (7)	0.0001*
No	87 (87)	99 (99))	186 (93)	
Presence ofMouth odour				
Yes	12 (12)	2 (2)	14 (7)	0.001*
No	88 (88)	98 (98)	186 (93)	
How many times do you brush your teeth per day?				
Once	61 (61)	73 (73)	134 (67)	0.049*
Twice	39 (39)	27 (27)	66 (33)	
What do you use to brush your teeth?				
Tooth brush only	68 (68)	52 (52)	120 (60)	0.020*
Chewing stick only	1 (1)	0 (0)	1 (0.5)	
Chewing stick and toothbrush	31 (31)	48 (48)	79 (39.2)	

Wilcoxon rank-sum test * Statistical significant

Table 3: Sex Variations in Physical and Biochemical Analysis of salivary constituents of subjects.

Constituents	Diabetic Patients (SD)	Non Diabetic Patients (SD)	All subjects (SD)	P value
Salivary Mean flow rate (ml/min)				
Male	0.32±0.13	0.68±0.32	0.55±0.32	0.0077*
Female	0.31±0.12	0.68±0.36	0.45±0.34	
Salivary PH				
Male	7.32±0.46	7.68±0.66	7.55±0.62	0.0081*
Female	7.11±0.70	7.66±0.65	7.32±0.32	
Glucose(mmol/L)				
Male	0.65±0.33	0.11±0,06	0.29±0.06	0.004*
Female	0.68±0.61	0.12±0.14	0.47±0.56	
Creatinine				
Male	171.2±26.6	0.65±0.09	60.1±83	0.00001*
Female	167.7±6.67	0.61±0.14	105.8±85	
Urea (mml/L)				
Male	10.4±5.6	0.861±0.38	4.2±5.66	0.0001*
Female	13.5±6.67	0.76±0.40	8.8±8.1	

Wilcoxon rank-sum test * Statistical significant

statistically significance. Salivary glucose, creatinine and urea was higher in subjects above 50 years but the difference were not statistically significant (Table 4).

Discussion

The physical and chemical properties of saliva are strongly associated with the changes in internal or external environment of the individuals. Patients with diabetes, therefore, show some changes in the saliva which can be a pointer to diagnosis and disease monitoring. In addition to the chemical and physical properties of diabetes patients, the present study revealed the association between salivary parameters, sex and age.

In this study, diabetes mellitus was found to be more frequent among men when compared women with male to female ration of 3:2. This finding is consistent with the reports of a United Kingdom based review by Siddiqui et al. which showed a higher prevalence of DM among males [17]. The sex variation of diabetes mellitus is attributed to lifestyle changes, predisposition to predisposing factors, genetics and environments [18,19]. This also showed that diabetes in more frequent among population of older age group which is consistent with the findings of Alva et al. 2017 who reported that the risk equation of diabetes is successful in middle age adult than young population [20].

Patients with diabetes mellitus often present with oral problems as a result of the disease process, associated complications and

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Table 4: Age Variations in Physical and Biochemical Analysis of some salivary constituents.

Constituents	Diabetic Patients (SD)	Non Diabetic Patients (SD)	All subjects (SD)	P value
Salivary Mean flow rate at different age category(ml/min)				0.226
<50yr	0.31±0.13	0.59±0.23	0.47±2.39	
>50yr	0.31±0.12	0.74±0.39	0.50±0.35	
Salivary PH at different age category				0.180
<50yr	7.10±0.61	7.78±0.66	7.50±0.70	
>50yr	7.22±0.64	7.59±0.64	7.40±0.67	
Glucose(mmol/L)				0.218
<50yr	0.670±0.818	0.12±0.14	0.335±0.603	
>50yr	0.67±0.356	0.10±0.06	0.409±0.386	
Creatinine				0.02
<50yr	161.22±27.9	0.645±0.135	68.83±81.93	
>50yr	172.40±34.79	0.642±0.09	93.96±89.61	
Urea (mml/L)				0.042
<50yr	11.83±6.23	0.81±0.41	5.49±6.8	
>50yr	12.89±6.62	0.83±0.42	7.38±7.75	

Wilcoxon rank-sum test * Statistical significant

medications. Consistent with other studies, this study found higher prevalence of oral symptoms among diabetes. More than one-third (38%) of diabetes patients present with oral symptoms such as had history of tooth ache, gum bleeding, oral malodour and taste impairment, this finding is in agreement with some other studies [13]. Tooth ache is usually a result of severe periodontitis and multiple periodontal abscesses seen in diabetes patients as a result of impaired immunity, vasculopathy and changes in salivary parameters. Changes in quantity and quality of saliva produced, tongue depappilation and vasculitis may be responsible for the taste impairment while oral malodour is usually attributed to acetone breath and poor oral hygiene which is more frequent among diabetic patients [13,21].

Various reports had showed that diabetic subjects have lower salivary flow rate compared to those without diabetes [8,22]. In the present study, the mean unstimulated salivary flow rate is 0.32+0.13 ml/min which was significantly lower than 0.68+0.32 ml/min of the non-diabetic patients. This result was similar to the findings of Hoseini et al. who reported 0.35+0.11 and 0.5+0.07 ml/min as salivary flow rate of diabetic and non-diabetic patients respectively [22]. Reduced salivary production in diabetic patients may be due to dehydration, effects of medication and neuropathy of the parasympathetic stimulation of the salivary gland in diabetic patients [22]. This leads to oral problems such as taste impairment, gingivitis, mucositis, halitosis and poor oral hygiene [13].

DM is associated with variations in saliva composition and secretion [21]. The pH which measures the degree of acidity or basicity of substances is also affected in diabetic patients [23]. In this study, we found a significantly lower (acidic) pH among diabetes participants. This is consistent with the findings of Seethalakshmi et al. 2016 who analyzed the saliva of 20 diabetic and 20 non-diabetic patients and observed a reduced pH among diabetic patients compared to control [24]. The acidity of saliva in diabetes mellitus patients may be due to organic acid generated following gluconeogenesis and impaired osmoregulation due to diabetic nephropathy. The pH is also significantly lowered (acidic) in females probably due to the effects sex hormones.

Salivary glucose concentration is a reflection of plasma glucose concentration. Consistent with other studies, salivary glucose of diabetic participants was significantly higher than that of the non-diabetes [12,23,25]. Primary saliva, from where the secondary saliva in the mouth is formed, is essentially an ultra-filtrate of the plasma and it's a direct reflection of the level of plasma glucose. Salivary urea is also significantly higher in males consistent with other studies. Higher blood sugar among males is due to male predilection of DM

Like salivary glucose, the concentration of urea and creatinine in saliva reflect the plasma values and are significantly higher in diabetic patients [26]. Increase plasma urea is a basic sign of renal problems. Consistent with scientific literature, salivary urea is significantly higher in diabetic patients [8,25]. Renal impairment (nephropathy) is not uncommon in diabetic mellitus; this may be responsible for the higher values. Higher urea level may also be found in higher protein diet and exercise. This study showed a higher urea concentration in saliva of females consistent with other studies.

Qualitative changes in saliva with respect to age are commonly reported in the literature [12,24,26]. In this study we report higher PH in subjects older participants above 50 years this may be connected to to renal impairment which tends to happen at older age group, Likewise, salivary glucose, urea and creatinine concentration was found to be significantly higher older individuals. Increasing age predisposing to renal problems may also be responsible to the findings.

Salivary analysis has showed significant variations among diabetic and non-diabetic patients, as revealed in this study which was done among African population. Also, the relationship between the salivary and plasma concentration of the substances measured further reaffirm the potential use of saliva in the diagnosis and monitoring of diabetic patients. This become especially in resource limited countries.

Clinical Significance

This study had shown recent African data on salivary parameters and oral findings among diabetes and non diabetes. Major findings

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were reduced salivary flow rate, increase salivary glucose, increased urea and creatinine concentrations among diabetes. The significant association between prevalence of oral lesions among diabetes as well as significant qualitative changes in saliva of diabetes is a potential non invasive tool of monitoring treatment outcomes of diabetes and also could enhance the multidisciplinary management of this distressing metabolic disease in our resource limited environment.

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