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Liver Biomarkers in *Diabetes mellitus*, Prediabetes and Periodontal Disease: Evidence of Triangular Correlation

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Abstract: It is known that patients with fatty liver disease and periodontal disease (PD) are at risk for developing diabetes mellitus (DM) and vice versa. However, evidence of any triangular correlation as well as epidemiological data from rural communities of low-mid income countries. This study evaluated the correlation and differences in average levels of blood sugar, liver biomarkers and PD indices among patients attending orodental clinic Volunteer hospital clients were classified into prediabetes, prediabetes-PD, diabetic-PD and control. Blood glucose levels (BGL), lipid profile and orodental examinations were investigated. Analysis included correlation of BGL with clinical attachment loss (CAL) and gingival recession (GR); as well as liver biomarkers. Gender differences in all assessed parameters were also determined. Results showed that BGL in groups strongly correlates with levels of CAL ($r = 0.74$), GR depths ($r = 0.72$), serum protein ($r = 0.88$) and total bilirubin($r = 0.71$). The PD indices also showed moderate to strong correlations with liver enzymes ($r = 0.44$), total bilirubin($r = 0.82$) andserum protein($r = 0.60$). Lipid profile was neither correlated nor significant, except total cholesterol being significantly higher in men ($p < 0.01$). Conclusion, there is considerable correlation between the triad of BGL, liver biomarkers and PD indices. This observation extends the knowledge of diabetes-periodontal two-way relationship to include liver functions. The non-significant higher dyslipidaemia in DM-periodontal co-morbidity relative to periodontal-prediabetes may indicate a pathophysiology different from non-periodontal-prediabetes, but affirms implication of liver and oral health in diabetes pathogenesis.

Key words: Diabetes · Dyslipidaemia · Liver Function Tests · Periodontitis · Periodontal Disease · Screening

INTRODUCTION

Periodontal disease (PD) describes a number of diseases of the periodontal tissues that result in attachment loss and destruction of alveolar bone [1]. There is compelling evidence that individuals with diabetes (In particular, type 2 diabetes) have a higher rate of occurrence of periodontal disease and/or periodontitis and vice versa [2-4]. The reciprocity of the link between T2DM and periodontal disease has been highlighted; such as periodontal infections significantly impact on diabetic control and diabetes being a major risk factor for the development and severity of periodontal disease [4]. The number of people living with DM in Nigeria is anticipated to rise to 4.84 million by the year 2030 [5]. Another report has this value pegged at 5.3 million by the same year 2030 [6]. Even more worrisome is the report that females in Nigeria may have a higher rate of prevalence than males based on fasting blood glucose levels [7] which has been observed in the study community [8]. The implications of such reported prevalence data for many Nigerian rural communities where little or no health facilities and/or interventions exist remains to be determined due to insufficient reports from surveys or studies.

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Studies on an association between periodontal disease (PD), with diabetes and dyslipidemia are conflicting. For example, the study by Almeida *et al*. [9] found no relationship between the occurrence and severity of chronic periodontitis (CP) in normal or T2DM participants. More recently, another study has indicated significant alterations in the lipid profile of patients with CP compared to healthy individuals [10]. Yet, the association between the three conditions (DM, dyslipidemia and PD) has been likened to a vicious circle – where PD results in enhanced systemic inflammatory status, predisposing to poor glycaemic control which in turn could lead to alterations in lipid profile [11-14].

As the metabolic hub in the body of living organisms, the liver and its enzymes play vital roles in the processing, distribution and regulation of the metabolism of key nutrients, including glucose. Abnormal elevation in liver enzymes activities has been reported in individuals with prediabetes, diabetes and cardiovascular diseases [15-18]. Dyslipidemia in diabetic patients is well known as one of the risk factors to cardiovascular complications [19-21].

In a priori review [22] evidence of prevalence of DM and periodontal diseases in Nigeria was established. The knowledge that patients with fatty liver disease and PD are at risk for developing DM and vice versa has also been established [17, 23 and 24].The need for research into factors influencing co-morbidity of both diseases was suggested. In line with this, the present study aimed to investigate the link between liver function markers, dyslipidaemia, DM, prediabetes (IFG/IGT), periodontal diseases and their inherent roles as risk factors to CVD.

MATERIALS AND METHODS

Ethical Considerations: Ethical approval was obtained from the local government office of the Ministry of Health in Kwale and the management of Eku Baptist Government Hospital, Delta State Nigeria. The individuals were contacted through churches and consultation via community focus groups. During each session, public lectures were followed by the provision of consent forms; consented individuals were then given the WHO STEPS questionnaire as well as an additional questionnaire specific for periodontal examination at the Dental Clinic in Eku Baptist Government hospital. Information gathered from these questionnaires included demographics, anthropometric measurements, status of orodental health, status of DM, history of previous screening or tests for DM or related conditions, etc.

Study Population, Design and Setting: The study population consisted of adults (Aged 20 – 70 years) recruited from the catholic hospital Abbi and Eku Baptist government hospital in Ndokwa West and Ethiope East local government areas respectively in Delta state, Nigeria. A total of 34 participants (18 males, 16 females) were enrolled in the study; blood samples were collected from participants for the assay of blood glucose levels (BGL) and biochemical parameters specific for ascertaining liver function. This was followed by periodontal examination to check for bleeding on probing, gingival recession and clinical attachment loss.

For the purpose of this study, prediabetes is defined as fasting BGL in the range of 5.5 - 6.9mmol L^{-1} (100 – 125 mg dL^{-1}) or random BGL in the range 7.8- 11mmol L^{-1} (140 – 199 mg dL^{-1}); diabetes is defined as fasting BGL =7.0mmolL^{-1}(= 126 mg dL^{-1}) or random BGL = 12 mmol L^{-1} (= 200 mg dL^{-1}). These cut-offs have been used in previous studies also forming part of the Pre-diabetes and Cardiovascular Complications Study (PACCS) [25-27] and are consistent with international position statement [28]. All blood tests including sugar, lipid profile and liver function tests were performed by staff of the Eku Baptist government hospital in accordance with the hospital's diagnostic laboratory protocols.

Periodontal status in this study was determined using three (3) parameters: bleeding on probing (BOP), gingival recession (GR) and clinical attachment (CA) loss. Periodontal disease was established as: presence of bleeding after probing, CA = 2 mm and GR = 3 mm. These parameters are often used as biomarkers in the determination of periodontitis [1]. All periodontal disease assessments were also performed by professional dentists in accordance with the procedures of the orodental clinic at Eku Baptist government hospital.

Statistical Analyses: Based on results from periodontal examination and blood glucose levels, participants were placed into four groups: Group 1 (Prediabetic individuals), Group 2 (Individuals with prediabetes and periodontal disease), Group 3 (Individuals with diabetes and periodontal disease) and Group 4 (Apparently healthy individuals). Results were expressed as mean ± standard deviation (SD). Multivariate analysis of variance (MANOVA) comparison was performed using turkey HSD method, results were considered significant at 95% confidence limit ($P<0.05$).

RESULTS

Descriptive Stats: In general, liver biomarkers appeared to show no significant differences between groups ($p > 0.05$). BGL is significantly different between groups – as may be expected, it is higher among Group 3 compared to the other three groups ($P < 0.05$), but there is no statistically significant difference in BGL between Groups 1, 2 and 4 ($P > 0.05$). Lipid profile also appeared to show no statistical significance between groups (Table 1).

Correlation Between Glycaemia and Periodontal Indices: The average levels of CAL and GR as indices of periodontal disease as well as of liver markers indicated by bilirubin, total protein and transaminases correlates well with blood glucose levels (Table 2). The mean values of CAL and GR in groups show unidirectional increase from non-periodontal-prediabetes to periodontal-prediabetes and highest in periodontal-diabetes (Fig. 1), which was not observed in liver biomarkers.

Evaluation of Gender Differences: Liver function parameters are not significantly different between genders when viewed overall (Fig 2; $p > 0.05$), although the transaminases appear slightly higher in males compared to females. Lipid profile is significantly different, especially total cholesterol being higher in males than females (Table 3).

Table 1: Descriptive statistics of liver biomarkers (P > 0.05)

			95% Confidence Interval	
Variables	Groups	Mean	Lower Bound	Upper Bound
Fasting blood sugar mmol/L	1	5.820	5.080	6.560
	2	5.850	5.224	6.476
	3	9.000	7.830	10.170
	4	5.200	4.244	6.156
Total cholesterol mg/dL	1	131.300	107.635	154.965
	2	144.357	124.357	164.358
	3	166.500	129.083	203.917
	4	139.833	109.282	170.385
HDL-cholesterol mg/dL	1	50.200	40.771	59.629
	2	44.429	36.459	52.398
	3	50.750	35.841	65.659
	4	42.667	30.494	54.840
Triglyceride mg/dL	1	81.600	38.603	124.597
	2	128.143	91.804	164.482
	3	164.750	96.766	232.734
	4	94.500	38.991	150.009
Aspartate aminotransferase U/L	1	23.170	-7.273	53.613
	2	39.379	13.649	65.108
	3	20.500	-27.635	68.635
	4	20.817	-18.485	60.119
Alanine aminotransferase U/L	1	21.620	14.501	28.739
	2	19.379	13.362	25.395
	3	18.550	7.294	29.806
	4	30.933	21.743	40.124
Alkaline phosphatase U/L	1	87.450	75.852	99.048
	2	82.071	72.270	91.873
	3	82.250	63.912	100.588
	4	72.800	57.827	87.773
Total protein g/dL	1	7.380	.506	14.254
	2	7.321	1.512	13.131
	3	7.625	-3.243	18.493
	4	16.883	8.009	25.757
Albumin g/dL	1	3.650	-1.680	8.980
	2	6.121	1.617	10.626
	3	3.550	-4.877	11.977
	4	8.167	1.286	15.047
Total bilirubin mg/dL	1	0.850	0.766	0.934
	2	0.900	0.829	0.971
	3	0.925	0.792	1.058
	4	0.800	0.691	0.909

Table 2: Correlation between blood glucose, liver markers and periodontal nexus

	BGL (mmol/L)	*CAL (mm)*	*Mean GR (mm)*
BGL (mmol L-1)	1.00		
CAL (mm)	0.74	1.00	
Mean GR (mm)	0.72	1.00	1.00
SGOT	0.17	0.61	0.65
SGPT	0.02	0.44	0.49
Alkaline Phosphates	-0.09	0.14	0.20
Total Protein	0.88	0.64	0.60
Albumin	-0.15	-0.30	-0.34
Total Bilirubin	0.71	0.82	0.84

Table 3: Blood sugar and lipid profile in gender groups

	Age	GR (mm)	BOP	CAL (mm)	TC*	HDL	TG
Male	39.89	2.33	1.06	1.89	161	51	107
Female	43.21	2.31	1.19	1.69	129	43	116

*p < 0.01

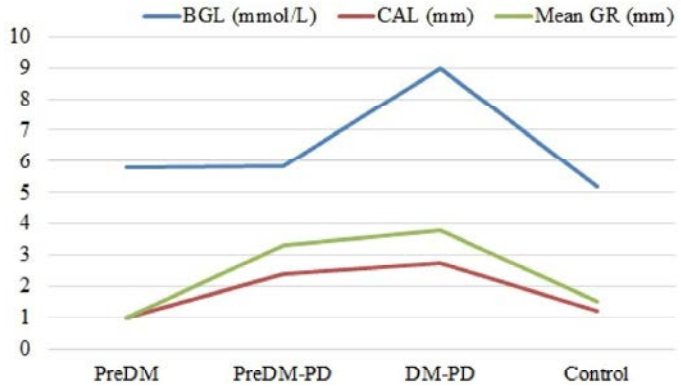

Fig. 1: Observation of gradual increase in PD indices from prediabetes to diabetes-PD

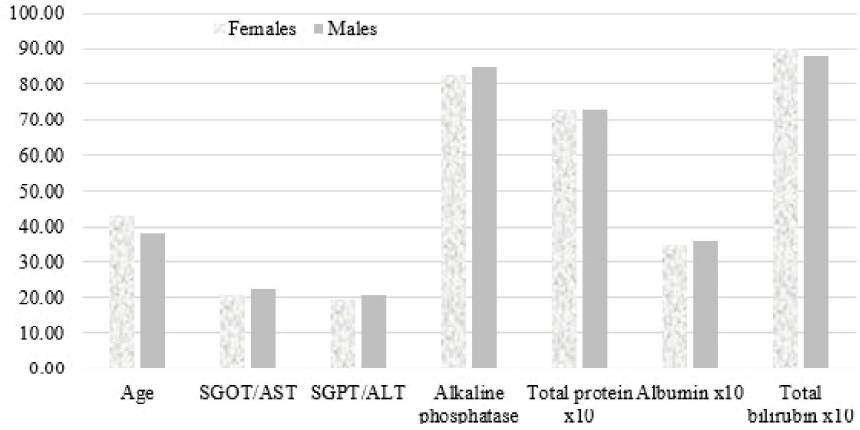

Fig. 2: LFT parameters in gender groups

DISCUSSIONS

Many studies have reported that prediabetes is associated with periodontitis and diabetes, but the association with lipid profile is not clearly understood. Few studies have attempted to investigate these rural communities [29, 30] and additional data will benefit the discourse. Further, fatty liver disease patients are at risk for developing type 2 diabetes and vice versa [24]. However, epidemiological data indicating disparity between diabetes and non-diabetes individuals in concomitant occurrence of dyslipidaemia and liver disease in the rural and sub-urban communities are lacking. Thus, investigation will help to elucidate the levels of blood

glucose levels impacts on the lipid profile of patients with diabetes, prediabetes and periodontitis and their risk to cardiovascular disease.

As was expected, subjects that were diabetic and had poor orodental health had significantly higher BGL compared with apparently healthy individuals (Group 4). The trend of increase in mean blood glucose concentrations among participants was: Group 4 (Apparently healthy control) < Group 1 (Prediabetes, no PD) < Group 2 (Prediabetes and PD) < Group 3 (DM and PD). Significantly higher blood glucose levels among diabetic participants in Group 3, alongside observed signs of periodontal disorder followed reported trend from other studies (Table 1).

For the assessment of periodontal health, the three parameters considered were: BOP, GR and CAL. Indications of GR were observed for most of the participants in Groups 2 and 3 compared with apparently healthy individuals (Group 4). Overall, all participants in Groups 2 and 3 who were either prediabetic or diabetic with periodontal disease had significant BOP. There was an increase in CAL by at least a 2-fold observed in individuals having combined diabetes-periodontal disease and prediabetes-periodontal disease compared with subjects that were only prediabetic or apparently healthy (Table 1). Furthermore, a calculated correlation coefficient of [r = 0.72] indicated that a strong positive correlation existed between blood glucose concentrations and periodontal indices (Fig. 1).

This observation is in line with reports from other studies where a link has been established between DM and poor periodontal health. In one report, diabetes is described as a major risk factor for periodontitis with possibility of up to three-fold increased risk of periodontitis in diabetic patients [31]. In fact, several studies have indicated a two-way relationship between diabetes and periodontal diseases and/or periodontitis. That is, diabetes had an adverse effect on periodontal health and PD had adverse effect on both glycaemic control and diabetes-related complications [11-14]. It is noteworthy that

- All diabetes patients in the study cohort have periodontal disease
- Prediabetes patients in this study have average blood sugar levels almost equal with the apparently healthy control groups (Table 1)
- The apparently health group has mean levels of PD indices seemingly higher than in prediabetes group (Fig. 1).

Implication of obesity to join in forming a triangular nexus is also speculated [32]. We have not evaluated obesity of participants in this particular study. Instead, we evaluated lipid profile and found neither correlations between other laboratory parameters, nor significant difference between disease groups. Nevertheless, our finding that subjects with PD and DM co-morbidity had at least two times increased risk for CAL, which strongly corroborates with positive correlation between BGL and GR depths. Perhaps, it is pertinent to emphasize that studies from other parts of the world have established a link between periodontal diseases and systemic disease conditions such as DM [11, 12, 14 and 31]. Therefore, what this reports contributes is more on the implication of liver biomarkers joining the diabetes and PD to constitute a triad relationship.

Secondary to investigation of correlations, attempt has been made to evaluate gender differences. The results showed that total cholesterol is better in women (Table 3) and liver enzymes appear to be relatively lower in women also (Fig. 2). This observation on lipid profile disagrees with the report of Kolovou *et al*. [33] but agrees in part that women are more likely to have lower HDL level no significant differences regarding triglyceride [34]. The observation on gender difference in liver also agrees in part with Poustchi *et al.* [35] who have reported a lower median level of AST in boys relative to girls [35]. Despite paucity in the availability of information on research studies associating DM, prediabetes and periodontal diseases among populations in Nigeria, results from the periodontal examinations conducted in this study has demonstrated the existence of a relationship between these diseases within a local context. There is need for more research to include wider populations across different regions of Nigeria to extend knowledge about co-morbidity with underlying mechanisms in different settings and using different measures of periodontal diseases.

Limitations of study included small sample size. However, findings contribute to existing limited data on gender differences in liver biomarkers. It had been identified that male and female human liver have been sparingly compared in terms of gender differences in acute hepatotoxicity that can be observed in vitro by comparing hepatotoxic drug effects; and that differences were found for certain parameters [36] including SGOT and SGPT being higher in males than females [35]. In this study, gender differences were found in level of total cholesterol ($p < 0.01$), but not in any of the liver function test parameters. Men have been reported to have higher

levels of TC and TG as well as lower level of HDL [37-39] thereby indicating that different levels of HDL (<35 mg/dL in men and <45 mg/dL in women) are critical for risk concerns [37]. Above all, the reported observation of moderate to strong correlation between the triad of BGL, liver functions and PD indices extends the knowledge of two-way relationship between diabetes and periodontitis to include liver function.

CONCLUSIONS

This study reports evidence of a moderate to strong correlations between the triad of blood sugar level, liver function test parameters and periodontal disease indices. Differences in blood glucose levels or stages of diabetes status may not on its owns translate into any statistically significant change in cholesterol profile or liver functions. Hence, routine LFT and lipid profile have yet to be considered as cost effective in screening and management of diabetes patients in low-mid income countries, especially in the absence of health insurance. The inference or recommendation from this study is that abnormality in any one of these x3 factors need to be seen as complications that may involve other two risk factors.

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REFERENCES

1. Highfield, J., 2009. Diagnosis and classification of periodontal disease. Aust. Dent. J., 54 Suppl: 1: S11-26. Make references like this style.
2. Borgnakke, W.S., 2016. Modifiable risk factors for periodontitis and diabetes. Current Oral Health Reports, 3(3): 254-269.
3. Borgnakke, W.S., 2016. “Non-modifiable” risk factors for periodontitis and diabetes. Current Oral Health Reports, 3(3): 270-281.
4. Saini, R., S. Saini and R.S. Sugandha, 2011. Periodontal disease: The sixth complication of diabetes. Journal of Family and Community Medicine, 18(1): 31. doi: 10.4103/1319-1683.78636. doi: 10.4103/1319-1683.78636.
5. Guariguata, L., D.R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp and J.E. Shaw, 2014. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract, 103(2): 137-149.
6. Shaw, J.E., R.A. Sicree and P.Z. Zimmet, 2010. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract, 87(1): 4-14.
7. World Health Organization. Noncommunicable Diseases Country Profiles 2011. 2011 27th June, 2017]; Available from: http://www.who.int/nmh/publications/ncd_profiles_report.pdf.
8. Nwose, E.U., V.M. Oguoma, P.T. Bwititi and R.S. Richards, 2015. Metabolic syndrome and prediabetes in ndokwa community of Nigeria: preliminary study. N Am J Med Sci., 7(2): 53-58.
9. Almeida Abdo, J., F.R. Cirano, M.Z. Casati, F.V. Ribeiro, V. Giampaoli, R.C. Viana Casarin and S.P. Pimentel, 2013. Influence of dyslipidemia and diabetes mellitus on chronic periodontal disease. J Periodontol, 84(10): 1401-1408.
10. Thomas, B., R.B. Prasad, S. Shetty and R. Vishakh, 2017. Comparative evaluation of the lipid profile in the serum of patients with type II diabetes mellitus and healthy individuals with periodontitis. Contemp Clin Dent, 8(1): 96-101.
11. Preshaw, P.M., A.L. Alba, D. Herrera, S. Jepsen, A. Konstantinidis, K. Makrilakis and R. Taylor., 2012. Periodontitis and diabetes: a two-way relationship. Diabetologia, 55(1): 21-31.
12. Kalra, M., P. Tangade, H. Punia, V. Gupta, H. Sharma and A. Jain., 2016. Assessment of two-way relationship between periodontal disease and gestational diabetes mellitus: A case-control study. Indian J Dent Res, 27(4): 392-396.
13. Gurav, A.N., 2016. Management of diabolical diabetes mellitus and periodontitis nexus: Are we doing enough? World J Diabetes, 7(4): 50-66.
14. Chee, B., B. Park and P.M. Bartold, 2013. Periodontitis and type II diabetes: a two-way relationship. Int J Evid Based Healthc, 11(4): 317-329.
15. Lazo, M., J. Rubin, J.M. Clark, J. Coresh, A.L. Schneider, C. Ndumele, R.C. Hoogeveen, C.M. Ballantyne and E. Selvin, 2015. The association of liver enzymes with biomarkers of subclinical myocardial damage and structural heart disease. J Hepatol., 62(4): 841-847.

16. Nguyen, Q.M., S.R. Srinivasan, J.H. Xu, W. Chen, S. Hassig, J. Rice and G.S. Berenson, 2011. Elevated liver function enzymes are related to the development of prediabetes and type 2 diabetes in younger adults: the Bogalusa Heart Study. Diabetes Care, 34(12): 2603-2607.
17. Ruckert, I.M., M. Heier, W. Rathmann, S.E. Baumeister, A. Doring and C. Meisinger, 2011. Association between markers of fatty liver disease and impaired glucose regulation in men and women from the general population: the KORA-F4-study. PLoS One, 6(8): e22932. doi: 10.1371/journal.pone. 0022932.
18. Sookoian, S. and C.J. Pirola, 2015. Liver enzymes, metabolomics and genome-wide association studies: from systems biology to the personalized medicine. World J Gastroenterol, 21(3): 711-725.
19. Farmer, J.A., 2008. Diabetic dyslipidemia and atherosclerosis: evidence from clinical trials. Curr Diab Rep, 8(1): 71-77.
20. Mooradian, A.D., 2009. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab, 5(3): 150-159.
21. Nepomuceno, R. and B.S. Villela, 2017. Dyslipidemia rather than Type 2 Diabetes Mellitus or Chronic Periodontitis Affects the Systemic Expression of Pro- and Anti-Inflammatory Genes. Mediators Inflamm, 2017:1491405. doi: 10.1155/2017/ 1491405.
22. Anyasodor, A.E., E.U. Nwose, R.S. Richards, P.T. Bwititi, K.A. Digban, L.I. Mudiaga, E. Aganbi and O. Ojodeme, 2017. Co-morbidity of diabetes mellitus and orodental diseases in Nigeria. Curr Diabetes Rev, 13(3): 289-299. doi: 10.2174/ 1573399812666160413114146.
23. Han, P., D. Sun and J. Yang, 2016. Interaction between periodontitis and liver diseases. Biomed Rep, 5(3): 267-276.
24. Wider, M.D., 2016. Metabolic syndrome and the hepatorenal reflex. Surg Neurol Int, 7:99. doi: 10.4103/2152-7806.194147.
25. Nwose, E.U., R.S. Richards and P.T. Bwititi, 2014. Cardiovascular risks in prediabetes: Preliminary data on "vasculopathy triad". North Am J Med Sci, 6(7): 328-332.
26. Oguoma, V.M., E.U. Nwose and P.T. Bwititi, 2014. Cardiovascular disease risk prevention: preliminary survey of baseline knowledge, attitude and practices of a nigerian rural community. North Am J Med Sci., 6(9): 466-471.
27. Oguoma, V.M., E.U. Nwose, T.C. Skinner, K.A. Digban, I.C. Onyia and R.S. Richards, 2015. Prevalence of cardiovascular disease risk factors among a Nigerian adult population: relationship with income level and accessibility to CVD risks screening. BMC Public Health, 15(1): 397. doi: 10.1186/s12889-015-1709-2.
28. American Diabetes Association, 2010. Diagnosis and classification of diabetes mellitus. Diabetes Care, 33(Suppl 1): S62-S69.
29. Andriankaja, O.M. and K. Joshipura, 2013. Potential association between prediabetic conditions and gingival and/or periodontal inflammation. J Diabetes Investig, 5(1): 108-114.
30. Azodo, C. and O. Amenaghawon, 2013. Oral hygiene status and practices among rural dwellers. Eur J Gen Dent., 2(1): 42-45.
31. Casanova, L., F.J. Hughes and P.M. Preshaw, 2014. Diabetes and periodontal disease: a two-way relationship. Br Dent J., 217(8): 433-437.
32. Levine, R.S., 2013. Obesity, diabetes and periodontitis--a triangular relationship? Br Dent J., 215(1): 35-39.
33. Kolovou, G.D., K.K. Anagnostopoulou, D.S. Damaskos, H.I. Bilianou, C. Mihas, H.J. Milionis, P.M. Kostakou and D.V. Cokkinos, 2009. Gender differences in the lipid profile of dyslipidemic subjects. Eur J Intern Med., 20(2): 145-151.
34. Gilani, S.Y., S. Bibi, N. Ahmed and S.R. Shah, 2010. Gender differences of dyslipidemia in type 2 diabetics. J Ayub Med Coll Abbottabad, 22(3): 146-148.
35. Poustchi, H., J. George, S. Esmaili, F. Esna-Ashari, G. Ardalan, S.G. Sepanlou and S.M. Alavian, 2011. Gender differences in healthy ranges for serum alanine aminotransferase levels in adolescence. PLoS One, 6(6): e21178. doi: 10.1371/journal.pone.0021178.
36. Mennecozzi, M., B. Landesmann, T. Palosaari, G. Harris and M. Whelan, 2015. Sex differences in liver toxicity-do female and male human primary hepatocytes react differently to toxicants in vitro? PLoS One, 10(4): e0122786. doi: 10.1371/ journal. pone.0122786.
37. Legato, M.J., 2000. Dyslipidemia, gender andthe role of high-density lipoprotein cholesterol: implications for therapy. Am J Cardiol, 86(12a): 15L-18L.

38. Santos, R.D., D.D. Waters, L. Tarasenko, M. Messig, J.W. Jukema, J. Ferrieres, J. Verdejo and C.W. Chiang, 2009. Low- and high-density lipoprotein cholesterol goal attainment in dyslipidemic women: The Lipid Treatment Assessment Project (L-TAP) 2. Am Heart J, 158(5): 860-866.

39. Goh, V.H., T.Y. Tong, H.P. Mok and B. Said, 2007. Differential impact of aging and gender on lipid and lipoprotein profiles in a cohort of healthy Chinese Singaporeans. Asian J Androl, 9(6): 787-794.