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SERUM LIPIDS AND GLYCATED HAEMOGLOBIN LEVELS IN PRE- AND POST-MENOPAUSAL DIABETIC SUBJECTS IN ENUGU, NIGERIA

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ABSTRACT: *Background: Studies have shown that poorly controlled diabetes mellitus result to significantly deranged lipid profile and atherogenic indexes in diabetic patients, thus they are at increased risk of dyslipidaemias. With respect to age and stages of a diabetic woman's life, there is much increased risk. Aim: The study was aimed to evaluate the lipid and glycated haemoglobin levels of pre- and post-menopausal women suffering from type 2 diabetes mellitus. Materials and Methods: A total of 148 known type 2 diabetic women (60 pre-menopausal and 88 post- menopausal women) and 90 healthy non-diabetic women (40 pre-menopausal and 50 post-menopausal women) were included in the study. HBA1c, total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) were determined using standard methods.Findings: This study showed that the HDL-C level was significantly lower ($p<0.05$) in both groups of diabetic women compared to their respective controls. In pre-menopausal diabetic women, with the exception of LDL-C, other lipid parameters and ratios (TC/HDL-C and TG/HDL-C) show significantly increased mean results ($p<0.05$) compared with that of the control. Increased TG, VLDL-C, and atherogenic indexes (TC/HDL-C and TG/HDL-C ratios), and reduced HDL-C levels ($p<0.05$) were the significant lipid alterations found in post-menopausal diabetic women compared to their age-matched controls. Furthermore, the study revealed that TC and HDL-C increased significantly ($p<0.05$) in post-menopausal diabetic women when compared with pre-menopausal diabetic women. Conversely, VLDL-C and TG levels together with the lipid ratios were found to decrease significantly ($p<0.05$) in post-menopausal diabetic women when compared with pre-menopausal diabetic women. The study also revealed that in pre-menopausal diabetic subjects HbA1c at $p<0.01$ correlated with some of the lipid parameters and the atherogenic indexes. Nonetheless, in the post-menopausal diabetic subjects no significant relationships ($p>0.05$) between HbA1c and all the lipid parameters and ratios were observed. Conclusion: This finding suggests that early detection and modification of poor glycaemic control and the accompanying specific lipid abnormalities may improve the health of the diabetic subjects.*

KEYWORDS: lipid profile, glycated haemoglobin, premenopausal, postmenopausal, diabetes mellitus

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INTRODUCTION

Abnormalities in lipid metabolism that are observed in the context of type 2 diabetes are among the major factors contributing to an increased cardiovascular risk (Vergès, 2015). Patients with type 2 diabetes have a combination of insulin resistance and dysfunctional β cells, but do not require insulin to sustain life, although insulin eventually will be required to control hyperglycaemia and keep glycated haemoglobin (HbA1c) below 7% in 90% of patients (Harvey and Ferrier, 2011). HbA1c reflects average plasma glucose over the previous 8 to 12 weeks (Nathan *et al*., 2007). It is used as an indicator for the state of glycaemic control, progression of the disease and development of complications in diabetic patients (Stolar, 2010). HbA1c is thus an independent risk factor of cardiovascular disease (CVD). Its measurement should be done routinely for every diabetic patient as recommended by the American Diabetes Association (ADA, 2003) at least twice per year in patients who have stable glycaemic control, and 4 times per year in patients who are not meeting their glycaemic control goals aiming to be < 7% to prevent the development and progression of complications.

Hyperglycaemia in diabetes causes accelerated advanced glycation end-products (AGEs) formation and has been linked to various diabetic complications like nephropathy, retinopathy, angiopathy, and neuropathy. The formation of AGEs is an irreversible process and glycation is a major cause of spontaneous damage to proteins in physiological systems. AGEs accumulate in tissues with age and their rate of accumulation is accelerated in diabetes (Popova e*t al*., 2010). Accordingly, hyperglycaemia leads to glycation of LDL particles. Glycation makes LDL particles more susceptible to oxidation (ie, glycoxidation) (Bohannon, 1992). Increased evidence suggests that impaired glycaemic homeostasis in diabetics has a direct influence on the propagation of atherosclerotic plaques (Boyle, 2007). This risk, however, can be reduced by good management, and control of both hyperglycaemia and dyslipidaemia (Windler, 2005).

Being female does contribute an added risk for gender-related problems. The ages and stages of a diabetic woman's life bring increased risk at every milestone, despite exquisite attention to glucose control (Chandrasekhar, 2016). Framingham Study suggests that female coronary heart disease (CHD) morbidity rates accelerate more quickly than do those of males after the age of 45 years (Lerner and Kannel, 1986). Other studies have also revealed that before menopause, women have reduced risk of developing cardiovascular disease than their male counterparts; however, this advantage is abolished after menopause (Rich-Edward *et al*., 1995, Couderc and Machi, 1999). Risk factors and complications of diabetes in perimenopausal women is significantly higher than in non-diabetic women. The subtle changes in body composition that occurs during menopausal transition negatively influences glucose metabolism

(Chandrasekhar, 2016).

Earlier epidemiologic reports have stated that diabetic women have a higher cardiovascular risk, as compared with diabetic men or non-diabetic women (Kannel, 1987; Barrett-Connor *et al*., 1991, Gu *et al*., 1998). According to Ng (2007), menopause is associated with increased cardiovascular disease and once women develop acute coronary symptoms, they have worse short- and long-term outcomes than men. Furthermore, it has been reported that cardiovascular risk profile coincides with menopause (Grundy *et al*., 2005, Alberti *et al*., 2006) and it is characterized by increases in some risk factors associated with this period such as visceral adiposity, hypertension, inflammatory markers plasma glucose and dyslipidaemia including atherogenic lipoproteins (Toth *et al*., 2000, Sites *et al*., 2002, Carr *et al*., 2003, Polotsky and Polotsky, 2010).

MATERIALS AND METHODS

Subjects:

A total of 238 women were randomly selected for this study. Women with type 2 diabetes (148) were recruited from Enugu State University of Science and Technology (ESUT) Teaching Hospital, Parklane, Enugu, Nigeria and age matched healthy control subjects (90) from hospital staff and volunteers. Ethical approval was sought and obtained from the Ethics Committee of Enugu State University of Science and Technology (ESUT) Teaching Hospital, Parklane, Enugu. Informed consent was duly obtained from each subject that participated in the study. With the aid of structured questionnaire, the participants' general characteristics such as age, weight, height, menopausal status, alcohol consumption, and medical history were obtained.

The subjects were categorised into 4 groups, on the basis of menopausal status and the presentation of diabetes mellitus as follows:

Group 1: 30 premenopausal women with diabetes within the age range of 31-46 years
Group 2: 44 postmenopausal women with diabetes within the age range of 50-71 years
Group 3: 20 premenopausal healthy non-diabetic women of comparable age with group 1
Group 4: 25 postmenopausal healthy non-diabetic women of comparable age with group 2

The premenopausal groups consist of women who were still having either regular or irregular menstrual cycles while the postmenopausal groups consist of women who had not experienced menstrual cycles in more than one year, according to the guideline on the diagnosis and management of menopause (Chaplin, 2016).

Inclusion and Exclusion criteria

Only patients with Type 2 diabetes mellitus on treatment (metformin) were considered eligible for the study, irrespective of duration of diabetes and complications. Also apparently healthy individuals who served as the control subjects were recruited in the study. Those that take alcohol or those on lipid lowering agents were excluded from the study.

Specimen collection and preparation

Fasting whole blood samples (6ml) were collected from each subject. About 2ml of the blood were dispensed into fluoride oxalate sample tube and EDTA sample tube for glucose estimation and HbA1c estimation respectively. The remaining part was dispensed into a plain sample bottle and kept at room temperature to clot, retract, centrifuged at 3000 rpm for five minutes, and the separated clear serum supernatants were transferred into sterile tubes and stored at -20^{o}C until analysis.

Statistical method

Statistical software, Statistical Package for Social Sciences (SPSS) Version 23, was used for the data analysis. The values were expressed as the mean ± standard deviation. Mean difference between groups was assessed by independent samples t-test. Association of two continuous variables was determined using Pearson's correlation coefficient (r). *P*-value of ≤ 0.05 was considered significant

RESULTS

Table 1: The mean fasting blood sugar and HbA1c levels ($p<0.05$) results of the pre- and post-menopausal diabetic patients were significantly higher when compared with that of control subjects. The investigation of the study subjects' lipid parameters showed that mean HDL-C level was significantly lower ($p<0.05$) in both diabetic groups (Group 1 and Group 2) in comparison with their respective age-matched non-diabetic subjects (Group 3 and Group 4). The levels of LDL-C, VLDL-C and TG were significantly higher ($p<0.05$) in premenopausal diabetic women when compared with that of the premenopausal non-diabetic women. In postmenopausal female diabetics the levels of cholesterol, LDL-C, VLDL-C and TG were not significantly different ($p>0.05$) from that of their non-diabetic control. Also, higher ($p<0.05$) atherogenic indexes (TC/HDL-C and TG/HDL-C ratios) were obtained in the diabetics when compared with their respective controls.

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Table 1: Biochemical parameters (Mean±SD) in pre- and post- menopausal diabetic and control subjects

	Pre-menopausal (N=100)			**Post-menopausal (N=138)**		
Parameter	**Diabetic (Group 1) n=60**	**Control (Group 3) n=40**	***p* value**	**Diabetic (Group 2) n=88**	**Control (Group 4) n=50**	***p* value**
FBS (mmol/l)	9.48±4.64	4.69±0.44	<0.001*	7.94±3.23	4.62±0.42	<0.001*
HbA1c (%)	7.16±1.02	5.15±0.87	<0.001*	7.61±1.25	4.97±0.90	<0.001*
TC (mmol/l)	4.86±0.86	4.67±0.56	0.228	5.25±1.04	5.13±0.63	0.395
HDL-C(mmol/l)	0.96±0.19	1.34±0.28	<0.001*	1.17±0.24	1.34±0.19	<0.001*
LDL-C (mmol/l)	3.30±0.83	2.85±0.58	0.004*	3.56±0.95	3.35±0.67	0.122
VLDL-C(mmol/l)	0.60±0.22	0.47±0.15	0.001*	0.51±0.22	0.45±0.13	0.024
TG (mmol/l)	1.33±0.49	1.05±0.34	0.001*	1.14±0.48	0.99±0.29	0.022
TC/HDL-C	5.29±1.47	3.57±0.60	<0.001*	4.56±0.94	3.91±0.69	<0.001*
TG/HDL-C	1.53±0.87	0.82±0.33	<0.001*	1.00±0.47	0.76±0.25	<0.001*

* - Mean difference significant at $p \leq 0.05$; n – Number of subjects in the group; SD – Standard Deviation; FBS – Fasting Blood Sugar; HbA1c – Glycated Haemoglobin; TC – Total Cholesterol; HDL-C – High Density Lipoprotein-Cholesterol; LDL-C – Low Density Lipoprotein-Cholesterol; VLDL-C – Very Low Density Lipoprotein-Cholesterol; TG – Triglyceride

Table 2: This shows the comparisons of biochemical parameters in pre- and post- menopausal diabetic women. HbA1c, TC, and HDL-C were found to increase significantly in postmenopausal diabetic women when compared with premenopausal diabetic women. VLDL-C and TG levels were found to decrease in post-menopausal diabetic women when compared with pre-menopausal diabetic women ($p<0.05$). Consequently, the atherogenic indexes were found to decrease significantly in postmenopausal diabetic women compared to that of premenopausal diabetic women.

Table 3: This shows the correlation analysis of HbA1c with lipid parameters and atherogenic indexes for the two groups of diabetic women. The Premenopausal diabetic subjects result showed that HbA1c had a strong negative correlation with HDL-C (r = -0.840, $p<0.001$). In addition, HbA1c at $p<0.01$ had a positive significant correlation with VLDL-C (r = 0.587), TG (r = 0.593) and TC/HDL-C (r = 0.779), TG/HDL-C (r = 0.714), and a positive significant correlation at $p<0.05$ with LDL-C (r=0.286). No significant statistical

relationship (p>0.05) was observed with TC (r=0.239). In the Postmenopausal diabetic subjects, there is no significant statistical relationship between the lipid parameters, including the atherogenic indexes, and the HbA1c (p>0.05)

Table 2: Biochemical parameters (Mean ±SD) in pre- and post- menopausal diabetic women

Parameter	Premenopausal n=60	Postmenopausal n=88	*p* value
FBS (mmol/l)	9.48±4.64	7.94±3.23	0.028*
HbA1c (%)	7.16±1.02	7.61±1.25	0.022*
TC (mmol/l)	4.86±0.86	5.25±1.04	0.016*
HDL-C (mmol/l)	0.96±0.19	1.17±0.24	<0.001*
LDL-C (mmol/l)	3.30±0.83	3.56±0.95	0.078
VLDL-C (mmol/l)	0.60±0.22	0.51±0.22	0.022*
TG (mmol/l)	1.33±0.49	1.14±0.48	0.023*
TC/HDL-C	5.29±1.47	4.56±0.94	0.001*
TG/HDL-C	1.53±0.87	1.00±0.47	<0.001*

* - Mean difference significant at $p \leq 0.05$; n – Number of subjects in the group; SD – Standard Deviation; FBS – Fasting Blood Sugar; HbA1c – Glycated Haemoglobin; FSH – Follicle Stimulating Hormone; LH – Luteinizing Hormone; TC – Total Cholesterol; HDL-C – High Density Lipoprotein-Cholesterol; LDL-C – Low Density Lipoprotein-Cholesterol; VLDL-C – Very Low Density Lipoprotein-Cholesterol; TG – Triglyceride

Table 3: Relationship between Hba1c and lipid parameters in pre- and post- menopausal diabetic women

	Premenopausal n=60		Postmenopausal n=88	
Parameter	r	*p* value	r	*p* value
HbA1c & TC	0.239	0.066	0.182	0.090
HbA1c & HDL-C	-0.840	<0.001**	-0.021	0.846
HbA1c & LDL-C	0.286	0.027*	0.177	0.100
HbA1c & VLDL-C	0.587	<0.001**	0.121	0.262
HbA1c & TG	0.593	<0.001**	0.121	0.263
HbA1c & TC/HDL-C	0.779	<0.001**	0.170	0.113
HbA1c & TG/HDL-C	0.714	<0.001**	0.131	0.225

r - Pearson Correlation Co-efficient, *Correlation significant at p<0.05; **Correlation significant at p<0.01; n –

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Number of subjects in the group; HbA1c – Glycated Haemoglobin; TC – Total Cholesterol; HDL-C – High Density Lipoprotein-Cholesterol; LDL-C – Low Density Lipoprotein-Cholesterol; VLDL-C – Very Low Density Lipoprotein-Cholesterol; TG – Triglyceride

DISCUSSION

Diabetes is a chronic illness that requires continuing medical care and patient's self-management education to prevent acute complication and reduce the risk of long term complication (American Diabetes Association (ADA), 2003). The report by United Kingdom Prospective Diabetes Study (UKPDS) revealed that cardiovascular disease was the major cause of complications in diabetes, and the predisposing factors include raised LDL-Cholesterol concentrations, low HDL-Cholesterol concentrations, elevated blood pressure and HbA1c concentrations, and smoking (Turner, 1998).

In this study, it was demonstrated that the premenopausal diabetic women (<50 years) presented with significantly increased LDL-C, VLDL-C and TG compared to the premenopausal non-diabetic women. Although an independent, inverse relationship between HDL and cardiovascular risk has been demonstrated beyond any doubt, the contribution of TG to cardiovascular risk has been underestimated. TG plays the role of a regulator of lipoprotein interactions and not role of an independent risk marker (Tiwari *et al*., 2015). This claim is supported by evidence that an increased plasma concentration of TG is associated with an increased population of small, dense LDLs and enhanced cholesteryl ester (CE) mass transfer from HDL to apolipoprotein B (apoB)-containing lipoproteins (Gue´rin *et al*., 2001).

It was also observed that there are significantly reduced HDL-C levels in the two female diabetic groups compared to their respective non-diabetic control subjects. This may suggest that the diabetics are at relatively higher risk of cardiovascular disease, in contrast to the non-diabetics. According to Flier (2008), the abnormalities of blood lipids are related mainly to different dietary habits of people, lifestyle and heredity along with other factors. Earlier studies had reported that type 2 diabetic patients had increased susceptibility to vascular disease associated with LDL-C. Conversely, Cardenas *et al*. (2004) found that HDL-C level was a major and independent risk factor, and had more relationship with the development of coronary artery disease (CAD) than total cholesterol and LDL-C level. In their work, de Freitas *et al*., (2011), also reported that low HDL-C was a risk factor for cardiovascular disease (CVD) of the elderly, whereas LDL-C showed no significant association with the development of CVD.

The lipid parameters comparisons of the diabetic women in this study revealed that HDL-C increased significantly in postmenopausal diabetic women when compared with premenopausal diabetic women. This

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is inconsistent with some previous studies which showed a gradual decrease in high density lipoprotein cholesterol in postmenopausal women (Jensen *et al*., 1990, Do *et al*., 2000). However, the observed trend is consistent with others showing a gradual increase between pre- and late perimenopausal women (Do *et al*., 2000, Hall *et al*., 2002). Similarly, studies on women with metabolic syndrome (MS) showed higher HDL cholesterol levels in postmenopausal women compared to premenopausal women (Derby *et al*., 2009, Fernandez and Murillo, 2016, Marchi *et al*., 2017). Fernandez and Murillo (2016) stated that it is possible that the observed increase in HDL-C in postmenopausal women could be due to a protective mechanism to counterbalance the deleterious effects of biomarkers associated with menopause but however studies are needed to confirm this theory. Furthermore, in some studies it was found that even though HDL cholesterol levels decrease with increased visceral fat and total weight, low HDL cholesterol levels are not a main feature of MS in postmenopausal women. With respect to age, HDL cholesterol levels seem to increase, and not decrease (Fernandez and Murillo, 2016). However, according to other researchers, because both menopause and lipids are highly associated with age, it remains unclear whether menopausal lipid changes are independent of age effects (Matthews *et al*., 1994, Do *et al*., 2000).

The results of this study showed that the atherogenic indexes were significantly higher in the different diabetic populations compared to their respective age- matched controls. This implies that these diabetics are at increased risk of CHD. This is supported by data from the Framingham study which showed that as the ratio of total cholesterol/HDL increases, so does the risk of coronary heart disease (CHD) (Kannel, 2007).

Given that TC and HDL-C were found to increase while TG levels was found to decrease in post-menopausal diabetic women when compared with pre-menopausal, the atherogenic indexes were found to decrease significantly in postmenopausal diabetic women compared to that of premenopausal diabetic women. In populations with low CHD incidences, average values of TC/HDL are below 4.0. In their study Stevens et *al*., (2004) stated that TC/HDL ratio is a superior measure of CHD risk than non-HDL cholesterol. It captures the protective effect of HDL cholesterol as well as the harmful effects of non-HDL cholesterol in a single parameter. Isolated elevation in triglycerides increases CHD risk, but its effect can be counteracted by the levels of HDL-C. Gaziano *et al*., (1997) reported that "the ratio of triglycerides to HDL was a strong predictor of myocardial infarction". TG/HDL-C ratio less than 0.87 is ideal, TG/HDL-C ratio above 1.74 is too high while TG/HDL-C ratio above 2.62 is much too high. In this study both TC/HDL and TG/HDL ratios were significantly above the ideal average values in the diabetic populations. This strongly indicates that these diabetics are at higher risk of cardiovascular disease.

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The fasting blood sugar and the glycated haemoglobin levels were found to be significantly higher in type 2 diabetic patients and thus confirm their hyperglycaemic state. HbA1c value ≤ 7.0 % is recommended to be appropriate for reducing the risk for cardiovascular complications (ADA, 2003). It has been estimated that reducing the HbA1c level by 0.2% could lower the mortality by 10% (Khaw *et al*, 2001).

This study additionally, revealed significant correlations between HbA1c and some lipid parameters and lipid ratios. The premenopausal diabetic subjects demonstrated highly significant inverse association between HbA1c and HDL-C, and significant strong positive correlations between HbA1c and the atherogenic indexes. Nonetheless, postmenopausal diabetic subjects showed no significant relationship between HbA1c and all the lipid parameters as well as with the lipid ratios. This finding suggests that the relationship between HbA1c and lipid parameters in the female diabetics may be countered by post-menopausal syndromes.

CONCLUSION

Carbohydrate-rich diet can have detrimental effects on glycaemic control, which plays a major role in the development of coronary artery disease and other macrovascular and microvascular complications. This study revealed that HbA1c correlated with some of the lipid parameters, together with highly significant association with the atherogenic indexes in pre-menopausal diabetic women. These findings indicate that HbA1c can be employed for screening high risk diabetic patients for early diagnosis as well as timely therapeutic intervention of dyslipidaemia and atherogenicity. Since HbA1c is an independent risk factor of CVD, HbA1C measurement should be done routinely for every diabetic patient as recommended by the American Diabetes Association (ADA, 2003).

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