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HYPERTRIGLYCERIDEMIA AND NON-HDL CHOLESTEROL IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

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ABSTRACT

The risk of diabetic nephropathy in type 2 diabetes is about 30-40%, and it is considered the leading cause of end-stage renal disease. This Study is aimed to determine the association between non-HDL cholesterol and inflammation in the development of diabetic nephropathy and to identify a possible predictor for diabetic nephropathy in type 2 diabetic patients. Eighty diabetic subjects were recruited for the study; 40 diabetic and normoalbuminuric were used as positive controls and another 40 diabetic and microalbuminuric as test group and these subjects were compared with 98 non-diabetic controls. Lipid profile, CRP, HbA1c, microalbumin, were estimated and result expressed as mean±SD. The difference in mean for Total cholesterol, LDL, triglyceride, were statistically significant when diabetic group were compared with the non diabetic control $P<0.01$. Our result show higher levels of total cholesterol, non-HDL-C, triglyceride, CRP and in diabetic groups when compared with controls ($p<0.01$). Our data shows a positive correlation between microalbumin and non-HDL cholesterol ($r=0.547, p<0.01$), microalbumin and triglyceride ($r=0.512, p<0.01$) Non HDL cholesterol and triglyceride should be considered as a potential risk factor and as a diagnostic biomarker to be used in conjunction with other biochemical markers for early diagnosis, assessment, and follow-up of diabetic nephropathy.

KEYWORDS: Diabetic nephropathy, normoalbuminuric, microalbumin, non-HDL-C, triglyceride, CRP.

INTRODUCTION

Diabetic Nephropathy (DNP) is a chronic disease caused by diabetes that leads to end stage renal diseases. Although various pathological mechanisms have been proposed till date on the progression of DNP, the exact cause of this disease is still unknown.[1] Atherogenic dyslipidemia of diabetes also known as diabetic dyslipidemia is characterized by elevated very low density lipoprotein (VLDL), small dense low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels, which constitute the lipid triad and are considered as traditional risk factors for cardiovascular disease (CVD).[2] Between 30% and 40% of patients with diabetes ultimately develop diabetic nephropathy, which is the commonest cause of end-stage renal disease requiring dialysis. Clinical and experimental evidence has shown that hyperlipidemia is a pathogenic factor for diabetic nephropathy. Among the different factors that may mediate the development and progression of diabetic nephropathy, hyperlipidemia is now considered an independent and major determinant. Elevated triglyceride-rich lipoproteins, a key factor of altered lipid profile in diabetic nephropathy, is present even in the earlier stages of renal disease. Previous observations revealed that diabetic patients with microalbuminuria have smaller LDL particles than those with normoalbuminuria, a relevant finding as small, dense LDL particles may be nephrotoxic.[3] Hyperglycaemia, hypertension, hypercholesterolaemia and protenuria are the most significant risk factors or markers in the development and progression of diabetic nephropathy in type II diabetic patients. It is important to explore other risk factors with potential therapeutic benefits in this group of patients.[4]

Elevated serum levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C) are strongly associated with increased risk for macrovascular events (e.g., myocardial infarction, ischemic stroke, and coronary mortality) among patients with T2DM. However, no consensus exists on possible mechanisms linking these individual lipid subfractions to microvascular complications.[5] To date, few studies have investigated the relative magnitude of association between individual lipid subfractions and diabetes-related MVCs.

Non-high-density lipoprotein cholesterol (non-HDL-C) concentration is a composite marker of several atherogenic lipoproteins, including low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and triglyceride .Non-HDL-C concentration can be measured by subtracting high-density lipoprotein cholesterol

(HDLC) concentrationfrom total serum cholesterol concentration and it may be used as a candidate biometrical equivalent to apolipoprotein B100 in diabetes.[6]

PATIENTS AND METHODS

The cross sectional study was conducted on diabetic Subjects attending the diabetes and general medicine clinic of federal medicine clinic of federal medical centre Owo, Ondo State, Nigeria. We enrolled 178 subjects (80 diabetic and 98 non-diabetic control) (45.5%) were females and 97 (54.5%) were males. The exclusion criteria were (1) patients who were already on lipid lowering drugs (2) females taking oral contraceptive pills (3) familial hypercholesterolemia (4) hypothyroidism (5) patients with chronic liver or kidney disease.

Ethical approval was obtained from the Federal Medical Centre (FMC) ethical review board, Owo, Ondo -state (Ethical Clearance Registration Number; FMC/OW/380/VOL.XXV/56). Informed consent were obtained from the study participants after a detailed explanation of the objectives of the study. After an overnight Fast, 5mls venous blood samples were drawn from patients, and all examinations were performed at 8.00 h after an overnight fast. The samples were divided into EDTA and plain bottles for each subject. Were allowed to clot, and serum was separated from the erythrocytes by centrifugation at 4°C and at 2000 ×g for 10 min. Total cholesterol, triglycerides, HDL were measured enzymatically using randox kits and biorad smartspec plus. Glycated hemoglobin concentration was determined using ion exchange resin method, using *Spectrum* HbA1c kit and the Method from EDTA anticoagulated blood and urinary microalbumin was determined using Agape microalbumin turbidlatex kit.

Anthropometric measurements including weight, height, waist, and hip measurements were obtained using standardized techniques. Heights were measured with a measuring tape to the nearest centimeter. Subjects were requested to stand upright without shoes with their back against the wall, heels together, and eyes facing forward. Weights were measured with a traditional spring balance that was kept on a firm horizontal surface. Subjects were asked to wear light clothing, and weight was recorded to the nearest 0.5 Kg. Body mass index (BMI) was calculated by using the formula: weight (Kg/height (m^2). Waist circumference was measured by using a nonstretchable measuring tape.

Data were reported as median or mean ± standard deviation for continuous variables and as percentage for categorical variables. Continous variables were compared usiung analysis of

variance (ANOVA) test. Bivariate correlation analysis was used to obtain the association between variables a value ≤ 0.05 was considered statistically significant.

Experimental Design

Study participants were divided into three groups

Group 2; Subjects (patient) with diabetes mellitus and micro albuminuria which are the major case group with micro albumin concentration above 20mg/l.

Group 1; Positive control subjects with diabetes mellitus and (normoalbuminuric) i.e with micro albumin concentration ≤20mg/l.

Group 0; Negative (normal) Control subjects without diabetes and normoalbuminuric

RESULT

The tables below show data comparing the mean and standard deviation Obtained from anthropometric parameters such as Age, Sex, Body mass index and Blood pressure (Table 1) the biochemical parameters like total cholesterol, LDL, HDL, triglyceride and Non HDL-cholesterol, Micro albumin, HbA1c and CRP (Table 2). Our result show higher levels of total cholesterol, non-HDL-C, triglyceride, CRP in diabetic groups when compared with controls ($p<0.01$). Our result shows a positive correlation between microalbumin and non-HDL cholesterol ($r=0.547, p<0.01$), microalbumin and triglyceride ($r=0.512, p<0.01$)

Table 1: Demographic characteristics of the study population

	GROUP 0	GROUP 1	GROUP 2
BMI	26.22 ± 4.38	27.39±6.83	29.42±4.21
AGE	54.12 ± 5.65	59.77±9.63	55.67± 8.54
WAIST CIRCUMFERENCE	35.58 ± 5.32	37.61 ± 7.54	40.18 ± 5.27
DIASTOLIC PRESSURE	78.63 ± 7.98	79.22±10.39	84.28±9.37
SYSTOLIC PRESSURE	114. 85 ± 8.72	126.67±11.53	130.71±18.99

Table 2: Biochemical Parameters of Different Study Groups

	Group 0	Group 1	Group 2
T. chol	3.56 ± 1.21	^{a}4.98±2.41	*^{a}6.06±2.34
Triglyceride	0.82 ± 0.39	*1.62 ± 0.57	*^{a}2.69 ± 1.05
LDL	1.84 ± 0.58	*3.01 ± 2.33	*3.29 ± 2.26
HDL	2.31 ± 0.72	1.93 ± 0.85	1.07 ± 0.85
Non HDL	1.84 ± 1.63	*3.21 ±2.49	*^{a}4.64±2.55
Micro Alb	11.51 ± 6.53	^{a}18.4±5.62	*^{a}65.42±42.29
HbA1c	6.49 ± 2.26	*8.90± 3.42	*^{a}11.49 ±8.24
CRP	3.54 ± 1.67	*5.29±4.22	*7.78±4.29

Statistical significance * $p<0.01$ compared with negative controls; $^{a}p<0.05$ compared to Group I patients)

DISCUSSION

Diabetic nephropathy is an increasingly important cause of morbidity and mortality worldwide. A large body of evidence suggests that dyslipidemia has an important role in the progression of kidney disease in patients with diabetes .Lipids may induce renal injury by stimulating Transforming growth factor-beta, thereby inducing the production of reactive oxygen species and causing damage to the glomeruli and glomerular glycocalyx.[7] In the present study, we have evaluated the pattern of lipid profile parameters in diabetic subjects and its correlation with CRP, HbA1c and micro albuminuria. Levels of HbA1c, CRP, Triglyceride, LDL cholesterol and non-HDL cholesterol differ significantly between patients and control, similarly we recorded a significant difference between the diabetic patient group and the positive control. Our study reveals high prevalence of hypercholesterolemia, hypertriglyceridemia, high LDL-C which are well known risk factors for cardiovascular diseases. The result of this study is in agreement with that reported by Ram et al.[8]

Insulin affects the liver Apo lipoprotein production. It regulates the enzymatic activity of lipoprotein lipase (LpL) and Cholesterol ester transport protein. All these factors are likely cause of dyslipidaemia in Diabetes mellitus with micro albuminuria. Moreover, insulin deficiency reduces the activity of hepatic lipase and several steps in the production of biologically active LpL may be altered in Diabetes mellitus.[9]

HDL-C is considered as a good cholesterol and elevated level are protective for coronary artery disease.[10] Microalbuminuria is another important screening tool for the detection of nephropathy. Furthermore, prospective studies have also confirmed a link between serum lipids and nephropathy.[11] In the current study, levels of HDL-C were not associated with the groups exhibiting micro albuminuria while non-HDL-C appear to be a better predictor of micro albuminuria, indicating association between non-HDL cholesterol and micro albuminuria. HDL-C was significantly and negatively associated with microalbuminuria in Saudi patients with diabetes and this also has been documented in other trial that higher HDL-C levels are associated with decreased likelihood of albuminuria among patients with diabetes.[12] Non HDL cholesterol represents and provides a single index of Apo lipoprotein B- containing lipoproteins. Hence LDL-C alone is not sufficient to estimate atherogenic risk in patients with elevated triglycerides. Furthermore LDL-C can be misleading if triglyceride concentration is >400mg/dl. In fact it has been shown that non-HDL cholesterol is a somewhat better predictor of CVD than LDL cholesterol[13] and in the present study, non

HDL-C was significantly associated with microalbuminuria in subjects that were studied.

CONCLUSION

Non HDL cholesterol should be considered as a potential risk factor and as a diagnostic biomarker to be used in conjunction with other biochemical markers for early diagnosis, assessment, and follow-up of diabetic nephropathy.

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