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Traditional lipid profile and underdiagnosis of chronic complications in diabetic population in Nigeria

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Abstract: *Background:* Traditional lipid profile is widely used in cardiovascular risk assessment in most of the health care centers despite the shortfall in its sensitivity to cardiovascular disease risk and clinical disease which had led to efforts to improve its sensitivity and specificity via the use of several lipid ratios to improve its diagnostic value. Therefore, this study evaluated the diagnostic relevance of traditional lipid profile, lipid ratios versus apolipoproteins in assessment of cardiovascular complications in Nigerian diabetic population. *Aim:* Evaluation of the diagnostic relevance of traditional lipid profile and lipid ratio versus Apolipoproteins in assessment of cardiovascular complications. *Methods:* 102 type 2 diabetic mellitus (DM) subjects (66 females and 36 males) and 100 control subjects of same age range (40-80 years) were recruited for this study which were further classified into nil apparent cardiovascular complication (63 subjects) and apparent cardiovascular complication (39 subjects) including peripheral neuropathy, retinopathy, cataract, stroke, foot ulcer, sexual dysfunction, glaucoma and ischemic heart disease. Lipid profile, Apo A and B analyzed with standard methods. *Result:* Apo-A1 is significantly more sensitive than other components of lipid profile and artherogenic indices in the subjects studied in diagnosis of cardiovascular diseases. *Conclusion:* Apo -A1 may be more sensitive than other components of lipid profile and artherogenic indices in screening for chronic complications of diabetes mellitus therefore may serve as a better surrogate marker of chronic complications of diabetes mellitus.
Keywords: APO-A1, Traditional Lipid Profile, Lipid Profile Ratios, Diabetes Mellitus, Cardiovascular Complication.

Introduction

Traditional lipid profile measures total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). These are then used to calculate LDL-C which has been found to correlate with the risk of cardiovascular disease (CVD). In Nigeria, LDL-C has been the primary lipid parameter for risk stratification and goal-directed therapy. Lifestyle measures to lower LDL-C are generally recommended, and statins (cholesterol lowering drugs) are used by millions of healthy people worldwide in order to lower LDL-C numbers. However, relying on LDL-C may be misleading.

Many individuals with high LDL-C have excellent prognosis and low risk of CVD, while many with normal or low LDL-C may be at high risk. Furthermore, low levels of total cholesterol and LDL-C are often associated with an increased risk of death. Therefore, there are pitfalls in LDL-C measurements in clinical practice. Indeed, scientific evidence suggests that the role of LDL-C as a risk factor may be overestimated. LDL and HDL lipoproteins exhibit a heterogenic distribution ranging from small, dense to larger and lighter particular structure in standard fractionation methods [1].

Recent experimental and epidemiological reports showed that small-sized LDL and HDL particles [Small-Dense LDL (sdLDL) and HDL_{3c} (SHDL)] are crucial players in pathophysiology of atherogenesis compared to larger particles [Large Buoyant LDL (LbLDL) and HDL_{2b} (LHDL)]. Particularly, sdLDL,

which are more susceptible to oxidation and conformational changes, accelerates inflammatory reactions and are associated with atheromatous plaque formation [1-2].

In the presence of excess of small dense sub fraction of LDL-C, total cholesterol level may not be raised, but the individual may have the disease process started. Moreover, atherosclerosis is initiated by apo lipoprotein B and the lesion progress by the deposition of lipids. It has been demonstrated by numerous studies over the last two decades that plasma lipid profiling using routine methods fails to distinguish lipid and lipoprotein abnormalities associated with cardiovascular diseases (CAD). It has been increasingly evident that analysis of lipoprotein sub-fractions rather than total plasma lipoprotein measurement is more informative in risk assessment for cardiovascular complications. Despite this finding, the use of traditional lipid profile for assessment of cardiovascular risk continues to be favored in Nigeria. Therefore this study intends to evaluate the diagnostic relevance of traditional lipid profile and lipid ratio in comparison to apolipoproteins in screening for chronic complications of diabetes mellitus.

Material and Methods

Study Design and Population: This is a comparative cross sectional study. A total of 102 type 2 DM subjects and 100 control subjects of same age range (40-80 years) were recruited for this study which were further classified into nil apparent cardiovascular complication (63 subjects) and apparent cardiovascular complication (39 subjects). Consenting participants were recruited from the endocrinology medical outpatient department of Federal Medical Centre Makurdi and Benue State University teaching, Makurdi, Benue State, Nigeria.

Ethical Consideration: Ethical approval was obtained from the Benue State University Teaching Hospital Makurdi and Federal Medical Centre Ethical Committee. Informed consent form was obtained verbally or in writing or both from the participants. Only consenting individual was recruited. Confidentiality was ensured throughout the study. Number code was allotted to each participant and result obtained from the blood analysis for the study was kept confidential (i.e. secret) such that no person can use the information to trace or know the patient.

Sample Collection and Biochemical Analysis: Sample of blood was drawn using fluoride oxalate and lithium heparin vacutainer for fasting lipid profile and Apo proteins respectively. The sample was centrifuged, separated and aliquot analyzed. Physical examination was done to elicit signs of chronic complication. Patients also filled a questionnaire aided by trained interviewers, about their symptoms.

Diabetes-related cardiovascular complication in the last 3-month were assessed with the aid of their medical records. Ethical approval was sought and obtained from the Medical Ethics Committee of Federal Medical Centre and Benue state university teaching hospital. Makurdi, Benue State respectively. Quality Control materials were included in every run. The intra assay CV for each run and inter assay CV was measured. Whenever the controls fall out of the control limits ±2SD, the run was repeated and source of error was sought and resolved. Apolipoproteins A-1 and B were analyzed using turbidimetric method while the lipid profile were analysed with enzymatic methods.

Statistical Analysis: Data analysis was done using the statistical package for social sciences (SPSS) windows version 21. Comparison of concentration of Cystatin-C, hbA1c and albumin-creatinine ratio of those with peripheral neuropathy and those without were analyzed with student t-test with mean expressed as mean ± SD. Significance was set at $P<0.05$. Receiver operating characteristic curve (ROC) of Cystatin-C and albumin-creatinine ratio was compared and statistically analyzed.

Results

Table 1 shows that Apo B/A1, triglycerides, LDL, non-HDL, non-HDL/HDL, Log TG/HDL, TC/HDL and LDL/HDL were significantly elevated ($P<0.05$) in diabetic subjects compared to the control. APO A1 and HDL were significantly elevated ($P<0.05$) in control compared to the diabetics subjects.

Table-1: Serum apolipoproteins, fasting lipid profile, atherogenic coefficient, atherogenic index in diabetic and control subjects (MEAN ±SD)

Parameter	Diabetic Subjects (N=102)	Control Subjects (N=100)	P-value
APO A1(mg/dl)	112.53±14.69	145.69±12.77	0.000**
APO B(mg/dl)	58.81±15.18	60.23±14.00	0.845
APO B/APO A1	0.53±0.12	0.41±0.87	0.000**
Total Cholesterol (mmol/l)	5.05±1.39	3.38±0.77	0.001*
Triglycerides (mmol/l)	1.75±0.85	0.45±0.21	0.001**
HDL (mmol/l)	1.00±0.25	1.12±0.37	0.302
LDL (mmol/l)	3.26±1.37	2.05±0.69	0.016*
TC/HDL	5.44±2.43	3.2±0.98	0.006**
LDL/HDL	3.45±1.64	2.01±0.93	0.011*
NON-HDL (mmol/l)	4.05±1.34	2.26±0.74	0.001**
NON-HDL/HDL	4.44±2.44	2.20±0.97	0.006**
LOG TG/HDL	0.22±0.30	-0.39±0.24	0.000**
* significant at P <0.05	* *significant at P <0.01		

Table-2: Serum apolipoprotein, fasting lipid profile, atherogenic coefficient and in diabetic subjects with and without cardiovascular complications (Mean ±SD)

Parameters	Control	No Cardiovascular Complication (N=39)	Cardiovascular Complication (N =63)
APO A1(mg/dl)	145.69±12.77	120.51±20.30 [a]	109.96±20.83[ab]
APO B(mg/dl)	60.23±14.00	65.62±19.23 [a]	61.17±25.07[b]
APO B/APO A1	0.41±0.87	0.53±0.14 [a]	0.55±0.24 [ab]
Total Cholesterol (mmol/l)	3.38±0.77	4.33±1.30 [a]	4.01±1.31 [a]
Triglycerides (mmol/l)	0.45±0.21	2.35±1.06 [a]	2.02±0.79 [ab]
HDL (mmol/l)	1.12±0.37	1.11±0.26	1.05±0.32 [ab]
LDL (mmol/l)	2.05±0.69	2.15±1.38	2.01±1.37
TC/HDL	3.2±0.98	4.36±2.60 [a]	4.16±1.94 [a]
LDL/HDL	2.01±0.93	2.18±1.98	2.24±1.71
NON-HDL (mmol/l)	2.26±0.74	3.22±1.41[a]	2.95±1.32
NON-HDL/HDL	2.20±0.97	3.3±2.60 [a]	3.16±1.9 [a]
LOG TG/HDL	-0.39±0.24	0.28±0.30 [a]	0.27±0.24 [a]
Values are expressed as mean ± SD, [a] = significantly different (P <0.05) from control, [b] = significantly different (P <0.05) from subjects with nil complication			

Table 2 shows that HDL was significantly increased (P<0.05) in subjects with control subjects compared with those with no cardiovascular complications while APO B,APO B/A1,Triglycerides,TC/HDL, non-HDL ,non-HDL/HDL and Log TG/HDL were significantly elevated in subjects with no cardiovascular complication compared with control subjects. APO A1 and HDL were significantly increased (P<0.05) in subjects with no cardiovascular complications and control subjects respectively compared to those that had cardiovascular complication while triglycerides, total cholesterol, TC/HDL , non-HDL/HDL and Log TG/HDL were increased with subjects with cardiovascular complication

than those without cardiovascular complication and control respectively while LDL/HDL and non-HDL were found to be elevated in cardiovascular complication compared to control.

Table-3: Area under the curve of receiver operating characteristic curve (roc) for APO A1 and HDL diagnostic sensitivity of cardiovascular complication

Test variables	Area under the curve	Sig.
APOA1	0.663	0.006**
HDL	0.057	0.236
* significant at P <0.05		

Fig-1: Area under the curve of Receiver Operating Characteristic (ROC) Curve.

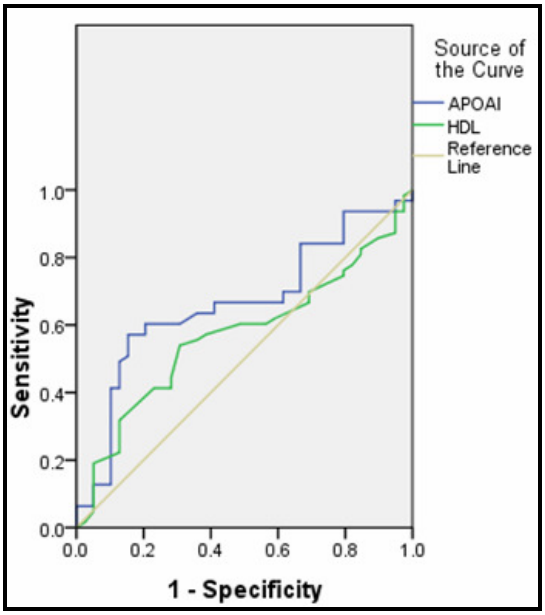

Table 3, the receiver operating characteristic (ROC) curve shows that APO A1 ratio showed significant (P<0.05) sensitivity to cardiovascular complication while HDL showed no significant (P<0.05) sensitivity to cardiovascular complication.

Table 4 indicates that the ROC curve shows that Total Cholesterol, Triglycerides, LDL, non-HDL/HDL, Apo B, ApoB/Apo A1 showed no significant (P<0.05) sensitivity to cardiovascular complication in the diabetic subjects studied.

Table-4: Area Under The Curve Of Roc Curve For Total Cholesterol, Triglycerides, LDL, NON-HDL/HDL, APO B, APOB/APO A1 diagnostic sensitivity and sensitivity of cardiovascular complication

Test variables	Area under the curve	Sig.
TC	0.427	0.214
TG	0.412	0.137
LDL	0.474	0.659
TC/HDL	0.498	0.967
LDL/HDL	0.512	0.839
NON-HDL	0.443	0.337
LOGTG/HDL	0.489	0.850
NON-HDL/HDL	0.498	0.967
APOB	0.451	0.405
APOB/APOA	0.510	0.871
* significant at P <0.05		

Fig-2: Area under the Curve of Receiver Operating (ROC) Curve.

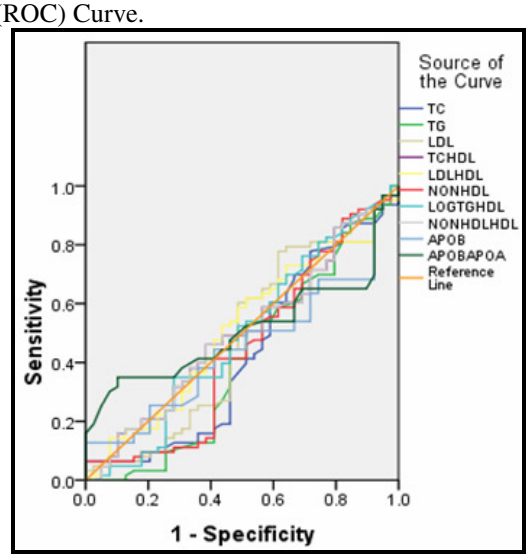

Table 5 shows that 28, 30 and 21 of the subjects have normal weight, overweight and obesed. Among the subjects with normal weight 21(80.2) and 7(19.8%) had cardiovascular and no cardiovascular complication respectively. Those that are overweight had 26(89.2%) and 4(10.8%) had cardiovascular and no cardiovascular complication respectively. Among the obese subjects 16(80.8%) and 39(38.2%) had cardiovascular and no cardiovascular complication respectively. There is no statistical (P<0.05) between those that had cardiovascular complication and those without complication with varying BMI.

Table-5: Cross Tabulation Of Body Mass Index (BMI) And Cardiovascular Complication				
BMI	Count (Frequency %)			P-value
	Apparent cardiovascular complication	No apparent cardiovascular complication	Total	
Normal Weight	21(80.2)	7(19.8)	28(100)	0.05
Over Weight	26(89.2)	4(10.8)	30(100)	
Obesity	16(80.8)	5(19.2)	21(100)	
Total	63(61.8)	39(38.2)	102(100)	
* Significant at P <0.05				

Table-6: Cross tabulation of hypertension and cardiovascular complication				
	Count (Frequency %)			
Hypertension	Apparent cardiovascular complication	No apparent cardiovascular complication	Total	P-value
Yes	51(69.9)	22(30.1)	73(100)	0.028*
No	6(40.0)	9(60.0)	15(100)	
Don't Know	6(42.9)	8(57.1)	14(100)	
Total	63(61.8)	39(38.2)	102(100)	
* Significant at P <0.05				

Table 6 shows that 73, 15 and 14 are hypertensive, not hypertensive and uncertain of their blood pressure status. Amongst the 73 that were hypertensive 51 (69.9%) had cardiovascular complication while 22 (30.1%) do not have complication, amongst 15 that do not have complication 6(40%) had cardiovascular complication and 9(60%) had no cardiovascular complication. Amongst those that do not know their status 6 (42.9%) had cardiovascular complication and 8(57.1%) had no cardiovascular complication. Cardiovascular complication was found to be statistically significant (P<0.05) among those with hypertension.

Discussion

Apo B/A1, triglycerides, LDL, non-HDL, non-HDL/HDL and Log TG/HDL were significantly elevated while APO A1 and HDL were found to be reduced in diabetics compared to control. This is consistent with studies done by Dixit et al; 2014 [3]. The main cause of diabetic dyslipidemia is the increased free fatty acid released from fat cells due to insulin resistance. The increased flux of free fatty acid into the liver promotes triglyceride production, which in turn stimulates increase VLDL-cholesterol production and secretion of ApoB [4]. Hyperinsulinemia is also associated with low HDL cholesterol levels [5-6]. The increased numbers of VLDL cholesterol particles and increased plasma triglyceride levels decrease the level of HDL cholesterol and increase the concentration of small dense LDL-cholesterol particles via processes: VLDL-transported triglyceride is exchanged for HDL-transported cholesteryl ester through the action of the cholesteryl ester transfer protein (CETP), which results in cholesterol rich VLDL remnant particles and triglycerides-rich, cholesterol-depleted HDL particles. The triglyceride-enriched HDL is subsequently hydrolyzed by hepatic lipase or lipoprotein lipase; Apo A-I dissociates from the reduced-size HDL, which is filtered by the renal glomeruli and degraded in renal tubular cell leading to reduced APO A-1 and HDL concentration [7-8].

The increased concentration of small dense LDL-cholesterol particles is explained by a similar lipid exchange. Increased levels of VLDL transported triglyceride enable CETP to promote the transfer of triglyceride into LDL in exchange for LDL-transported

cholesteryl ester. The triglyceride-rich LDL undergoes hydrolysis by hepatic lipase or lipoprotein lipase, which results in lipid depleted small dense LDL particles [9]. More so, decreased APO A1 and HDL was found more in subjects with cardiovascular complication than those without .Apo-A1 is the Apo protein of HDL. Several epidemiological studies have suggested reduced HDL-c is associated with poor cardiovascular outcome [10].

It primarily mediates the process of reverse cholesterol transport (RCT) by scavenging cholesterol from peripheral cells, including from macrophages in atherosclerotic plaque, returning it to the liver for further metabolism and excretion [11]. In addition, HDL promotes endothelial function and has demonstrated anti-inflammatory, anti-oxidative, anti-thrombotic, and anti-diabetic properties, all of which should, conceivably, protect against vascular complications [12]. Therefore, HDL may facilitate diabetic complication due to loss of these functions.

Triglycerides, total cholesterol, TC/HDL and LDL/HDL, non-HDL, non-HDL/HDL and Log TG/HDL were increased with subjects with no cardiovascular complication than those with cardiovascular complication. This may probably be as a result of non-specificity of these to the cardiovascular manifestation. Though they are indicators of diabetic dyslipidemia and atherosclerosis but may probably not be very useful in stratification of cardiovascular complication hence increase did not correlate with presence of cardiovascular complication. The measurement of TG in the evaluation of cardiovascular (CV) risk has long been associated with multiple limitation. This include skewed distribution that necessitates categorical definitions or log transformations, increasing variability with rising TG levels, inverse association with high-density lipoprotein cholesterol (HDL-C)/ apolipoprotein (Apo) AI and finally its way of measurement; fasting versus non-fasting.

It is well recognized that as a component of the metabolic syndrome, a high triglyceride level contributes to cardiovascular risk [13]. However, the extent to which elevated triglycerides constitute a direct risk for Cardiovascular diseases (CVD) or more likely represent a marker for other lipoprotein abnormalities associated with CVD risk is unknown and has been widely debated. Higher level of triglycerides were rather associated with pancreatitis.

Receiver operating curve shows that APO-A1 and HDL-c has area under the curve to be 0.663 and 0.057 respectively which means APO-A1 has 66%(sensitivity%) chances of confirming that a patient that had cardiovascular complication actually had cardiovascular complication while HDL in contrary has 5% (sensitivity%) chances of confirming that a patient that had cardiovascular complication actually had cardiovascular complication.

Therefore, this study shows that APO-A1 may serve as a better screening tool for cardiovascular complications of diabetes mellitus than HDL-c in our environment. On the contrary Total Cholesterol, Triglycerides, LDL-c, Non-HDL/HDL, Apo B, ApoB/Apo A1 showed no significant sensitivity to cardiovascular complication in subject studied. Cardiovascular complication was found to be statistically significant among those that had hypertension than those that had no apparent cardiovascular complication. This is consistent with study by Horr et al [14].

Hypertension and diabetes mellitus are common co-morbidities, thus both are component of metabolic syndrome. Hypertension is twice as frequent in patients with diabetes compared with those who do not have diabetes and up to 75% of CVD in diabetes may be attributable to hypertension leading to recommendations for more aggressive treatment (i.e., reducing blood pressure to <130/85 mm Hg) in persons with coexistent diabetes and hypertension [14].

Diabetes mellitus is a state of chronic hyperglycemia which predispose to glycotoxicity and lipotoxicity via several altered biochemical cascade which involves inflammation, oxidative stress and glycation of biomolecules which leads to atherosclerosis which causes vascular

dysfunction characterised by increased vascular smooth muscle proliferation, arterial stiffness, increased vascular tone and decreased vasodilatation as well as exaggerated activation of renin angiotensin aldosterone system ultimately leads to hypertension.

Conclusion

Apo -A1 may be more sensitive than other components of lipid profile and artherogenic indices in screening for chronic complications of diabetes mellitus.

Recommendation

Apolipoprotein A1 is a simple biochemical tools which should serve as good surrogate biochemical markers of cardiovascular complication. Thus can serve not only for screening for diabetic dyslipidemia but chronic complication as well.

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