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Increased high density lipoprotein cholesterol in adult nephrotic syndrome in Nigeria

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Summary
Forty-eight adult subjects consisting of 28 patients with nephrotic syndrome and 20 control subjects were studied. The plasma levels of high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol were all significantly elevated in the patients with nephrotic syndrome. The elevations in plasma total cholesterol and triglyceride concentrations and the ratio of LDL cholesterol/HDL cholesterol were also significant. On the other hand, there was a significant reduction in the ratio of HDL cholesterol to total cholesterol in the nephrotics. Our results suggest altered lipid and lipoprotein metabolism in adult nephrotic syndrome. The significant increase in low density lipoprotein cholesterol and the reduction in the ratio of HDL cholesterol to total cholesterol, despite the high HDL cholesterol, probably suggests an increased risk for developing coronary heart disease in Nigerian adults suffering from nephrotic syndrome. It is therefore suggested that patient-management strategies for nephrotic syndrome should include lowering of cholesterol by dietary and/or pharmacological therapies.

Keywords: *HDL, Cholesterol, Coronary Heart Disease, Nephrotic Syndrome*

Résumé
Quarante-hit (48) sujets adultes constitues de vingt-huit (28) patients ayant le syndrome nephrotique et 20 sujets controles ont ete etudies. Les taux de plasma des Lipoproteines de Forte Densite (HDL) du cholesterol, Les lipoproteins a Forte Densites (LDL) du cholesterol, et les lipoproteines de tres faible Densite (VLDL) du cholesterol, ont ete significativement eleves chez les patients ayant le syndrome nephrotique. Les elevations du taux total de cholesterol, des concentrations de triglycerides et des ratio LDL du cholesterol/HDL du cholesterol dans le plasma ont été significatifs. D'un autre cote, il y avait une reduction significative dans le ratio du HDL du cholesterol et le taux total de cholesterol chez les patients nephrotiques. Nous resultats sugerent une alteration du metabolism des lipides et lipoproteine chez les adultes ayant le syndrome nephrotique. La croissance significative des lipoproteines à faible densites du cholesterol et la reduction dans le ratio des HDL du fort taux de HDL du cholesterol suggere probablement un risque de developer les maladies cardiovascularies chez les adultes Nigerians ayant le syndrome nephrotique. Il est par consequent suggeré que la strategie de gestion des patients ayant le syndrome nephrotique devrait inclure la reduction du cholesterol par le regime et/ou par les therapies parhacologiques.

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Introduction

Nephrotic syndrome is a disease condition resulting from alterations in the structural and functional integrity of the glomerular capillaries of the kidney. The glomeruli are damaged and they become permeable to plasma proteins especially albumin and probably other blood components. Nephrotic syndrome (NS) could be of unknown cause (i.e., idiopathic or primary NS) [1] or from secondary consequences of infections (such as malaria, filariasis, schistosomiasis) and hepatitis viruses, diabetes mellitus, lymphoma, leukaemia and use of skin lightening creams, [1,2,3].

Hyperlipidaemia is a consistent feature of the nephrotic syndrome [4,5,6]. Various lipid and lipoprotein abnormalities have been found in nephrotic syndrome regardless of its aetiology [4,5,6]. In the Nigerian community there is scanty information on lipid and lipoprotein changes in adult nephrotic syndrome. A few studies have been carried out in childhood or on heterogeneous group (adult and children together) of nephrotic syndrome [7-11]. Most of these studies however did not measure all the lipoprotein fractions. Abdurahman *et al.* [8] reported increased concentrations of cholesterol and triglyceride in Nigerian children with NS, but did not measure any lipoprotein cholesterol fractions. Agbedana *et al.* [9] estimated only the high density lipoprotein cholesterol fraction among other lipid parameters in childhood nephrotic syndrome and found it significantly reduced, while Arije *et al.* [11] in their own study on a heterogenous group of patients found a reduced HDL cholesterol level.

Some studies have also been carried out on animals with induced nephrotic syndrome [12,13]. Marshall *et al.* found HDL cholesterol to be increased in nephrotic rats while Agbedana *et al.* [13] investigated specific lipid alterations in different tissues of nephrotic rats and found excessive cardiac lipid deposition in nephrotics. The nephrotic rat differs from the nephrotic humans in the lipoprotein distribution of cholesterol. The LDL carries the bulk of cholesterol in man, whereas most cholesterol is found in HDL in the rat [14]. Despite this difference, the qualitative changes in lipid metabolism that characterise the nephrotic syndrome are quite similar in both animal and human species [15]. However the data from animal species cannot be directly extrapolated to humans. While the HDL cholesterol level or ratio of HDL to total cholesterol are increased in neprotic rats [13] they are either unchanged or decreased (5) in patients with NS.

Lipoprotein metabolism in the nephrotic state may be influenced by age [8], severity of the disease [16], dietary habit and nutritional status [17] and aetiology (18) of the disease. There may be differences in the mechanism of hyperlipidaemia in human and animal species [12].

Generally, there is low prevalence of coronary heart disease (CHD) in black Africa [19] because of their low serum lipid levels [19,20]. However, the study by Erasmus *et al.* [10] suggested that Nigerians with nephrotic syndrome may represent a risk group for the development of ishaemic heart disease. Evidence from epidemiological and population studies has shown that lipoprotein metabolism is of interest in the diagnosis and treatment of atherosclerosis [21,22].

Atherosclerosis is characterised by a progressive thickening of the inner layer of the arterial wall caused by the localised deposition of lipid and cellular material resulting in reduced blood flow and weakening of the affected arteries.

Many studies using different approaches have suggested that elevated HDL and low LDL are anti-atherogenic, while reduced HDL and elevated LDL level are atherogenic and therefore associated with increased risk of coronary heart disease (CHD) [22,23]. The ratios of HDL cholesterol to total cholesterol and LDL cholesterol to HDL cholesterol were identified as better markers of risk of atherosclerosis [23,24]. Reduced ratio of HDL cholesterol to total cholesterol and increased ratio of LDL cholesterol to HDL cholesterol are regarded as being atherogenic [23,24].

This study is aimed at measuring the plasma lipoprotein cholesterol fractions and the atherogenic ratios in Nigerian adult nephrotics, with a view of assessing the risk for developing CHD among adult patients with nephrotic syndrome in Nigeria, a community where there is generally a low prevalence of CHD.

Patients, materials and methods

Subjects

Twenty-eight (20M,8F) adult patients suffering from nephrotic syndrome attending the Renal Clinic of the University College Hospital (UCH), Ibadan, were studied. Their ages ranged between 14 and 45 years with a mean value of 24.0 ± 1.6 years. Criteria for diagnosis were protein excretion exceeding 3.5 g/day or dipstick proteinuria of 3+ or 4+ level with presence of oedema and plasma albumin concentration of less than 2.5 g/dl.

The control subject were 20 (13M, 7F) age and sex-matched normal blood donors and subjects attending Neurology and Chest clinics who were neither hypertensive nor suffering from any systemic disease. Their ages ranged from 21 to 50 years with a mean of 28.0 ± 2.5 years.

Sample collection

After an overnight fast, 10 ml blood samples were collected by venipuncture into bottles containing EDTA (1 mg/ml) from both the patients and control subjects. The bottles were pre-chilled in an ice bath to prevent auto oxidation of the lipids. The samples were immediately centrifuged and the plasma kept at -20° for the lipid and lipoprotein cholesterol determinations.

Method

Separation of plasma HDL was done by the precipitation technique using heparin according to the method of Burstein and Samaille [25]. The total and HDL cholesterol concentrations were determined by the method of Searcy and Berquist [26]. Plasma TG concentration was estimated using the method of Gottfried and Rosenberg [27]. LDL and VLDL cholesterol concentrations were calculated using the Friedwald's formulae [28]

$$\text{i.e., } LDLchol = Tchol - (HDLchol + \frac{TG}{5})$$

$$\text{and } VLDL_{chol} = \frac{TG}{5}$$

Where Tchol = Plasma total cholesterol

HDL_{chol} = High density lipoprotein cholesterol

LDL_{chol} = Low density lipoprotein cholesterol

$VLDL_{chol}$ = Very low density lipoprotein cholesterol

TG = Triglyceride

Statistical analysis

The means and standard error of means (SEM) were calculated using standard methods. Pairwise comparisons were made using Student's t-test and $P<0.05$ was regarded as significant.

Results

As shown in Table 1, the plasma Na^+, Cl^-, HCO^-_3, total protein and albumin in the patients with nephrotic syndrome were significantly reduced ($P< 0.01$) while the changes in K^+ and creatinine concentrations were not significantly different when compared with the corresponding values in the control group. On the other hand, the urea concentration was significantly increased ($P < 0.01$) in nephrotic syndrome when compared with control values.

Table 1: Selected biochemical parameters in test and control subjects

Parameters	Nephrotic Syndrome	Control	*P*
Na^+ (mg/100 ml)	133.6 ± 9.6 (21)	139.9 ± 1.0 (15)	< 0.001
K^+ (mg/100 ml)	3.9 ± 0.1 (22)	3.9 ± 1.0. (15)	N.S
Cl^- (mg/100 ml)	100.3 ± 0.7 (21)	105.7 ± 1.0 (15)	< 0.001
HCO_3^- (mg/100 ml)	19.3 ± 0.4 (21)	26.1 ± 1.0 (14)	< 0.001
Urea (mg/100 ml)	62.1 ± 7.3 (23)	26.4 ± 3.9 (16)	<0.001
Creatinine (mg/100ml)	1.7 ± 0.3 (13)	1.1 ± 0.1 (14)	N.S
Total protein (g/100 ml)	5.1 ± 0.2 (22)	7.8 ± 0.3 (15)	< 0.001
Albumin (g/100 ml)	1.8 ± 0.1 (21)	4.2 ± 0.2 (14)	< 0.001

N.S. = Not Significant
All values are means ± SEM with number of subjects in parentheses.

Table 2 shows that mean values for total cholesterol and triglyceride concentrations were significantly increased in the patients with nephrotic syndrome ($P< 0.001$) when these are compared with the corresponding control

values, the percentage increases were 152% and 334%, respectively.

Table 2: Total cholesterol, Triglyceride and lipoprotein cholesterol concentrations in nephrotic and control subjects.

	Nephrotic syndrome	Control	% Change	*P = Values*
	n = 28	n = 20		
Age	24 1 ± 1 6	28.3 + 2 1		(NS)
T chol (mg/dl)	361 0 + 33 0	143.0 + 6.7	+152	<0.001
TG(mg/dl)	282 0 + 39.0	65 0 + 6.6	+334	<0 001
HDLchol (" ")	52 0 + 4 1	38 0 + 3.9	+37	<0 05
LDLchol (" ")	254 0 + 30 0	92.0 + 6 1	+176	<0.001
VDLchol (" ")	56 0 + 30 0	13.0 + 1.3	+331	<0 001
HDLchol/T-chol	0 16 + 0.02	0.264 + 02	-36	<0.001
LDLchol	5 3 + 0.6	3 0 + 0 02	+77	<0.001

N S = Not significant
Values are means ± SEM

Similarly the mean HDL cholesterol, LDL cholesterol and VLDL cholesterol concentrations were all significantly elevated *(P<0.05, P<0.001 and P<0.001,* respectively*)* in the patients with nephrotic syndrome. The corresponding percentage increases were 37%, 176% and 331%, respectively, when compared with the respective control values. In our patients, the calculated, ratio of HDL cholesterol to total cholesterol was significantly reduced (P< 0.001 and 36% reduction), while that of LDL cholesterol to HDL cholesterol was significantly elevated (P<0.001 and 77% increase*)* when compared with the corresponding control values.

Discussion

The findings in this study have demonstrated abnormally high plasma levels of total cholesterol, trigylceride, HDL cholesterol, LDL cholesterol and VLDL cholesterol in Nigerian adult nephrotics. The mean plasma total cholesterol and trigyceride levels were significantly elevated with increases of up to 152% and 334%, respectively, above control values. This is a consistent feature of lipid abnormality in nephrotic syndrome.

Similar result of raised mean plasma total cholesterol and triglyceride concentrations were reported in childhood nephrotic syndrome by Abdurrahman *et al.* [18] and Agbedana *et al.* [9]. The observations of high levels of LDL cholesterol and VLDL cholesterol in this study are also similar to some earlier reports [29,30], but the significantly high level of HDL cholesterol observed was at variance with those of others [10,11, 31]. Ohta and Matsuda [29], however, also found increased HDL cholesterol level in their patients. This variance may be due to difference in severity of the disease and disparity in age of patients employed.

Another plausible explanation for the variation of high, low or normal HDL cholesterol is the presence or absence of chronic renal failure [32]. It was postulated that HDL cholesterol does not increase in the patients with chronic renal failure (CRF) because it is probably lost in their urine. In the present study, chronic renal failure was not a common feature in majority of the patients as the percentage of CRF was 3.5%. A 24-hour urinary estimation of lipid losses is however needed to confirm any differential loss of HDL-like particles in nephrotic syndrome patients with different aetiology.

The risk of coronary heart disease (CHD) in nephrotic syndrome has been controversial [33,34]. Several reports have suggested the importance of determination of lipoprotein distribution of cholesterol as well as total plasma cholesterol and triglyceride in nephrotic syndrome in predicting the risk of atherosclerotic heart disease. Low levels of HDL cholesterol and elevated levels of plasma total cholesterol and TG have been reported to be positively correlated with the risk of developing ishchaemic heart disease [21,24]. The ratio of HDL cholesterol to total cholesterol has been identified as a better index for the risk of atherosclerosis than absolute levels of HDL cholesterol [23,24]. In this study, the ratio of HDL cholesterol to total cholesterol has been identified as a better index for the risk of atherosclerosis than absolute levels of HDL cholesterol [23,24] observed. Significant decreases in percentage HDL cholesterol contribution to total cholesterol were similarly reported in other studies and found to accelerate atherosclerotic coronary artery disease [24]. This study seems consistent with the earlier suggestion by Erasmus *et al.* [10] that Nigerians with the nephrotic syndrome represent a risk group for accelerated atherogenesis and ischaemic heart disease. Sestak *et al.* [35] also gave an indirect evidence from their rat model studies that in humans and species susceptible to atherosclerosis, nephrotic syndrome may increase the risk of atherosclerosis.

Our findings probably suggest that there may be an increased risk of coronary heart disease among Nigerian nephrotics that live up to adult age and patient management strategies should include lowering of cholesterol by dietary and /or pharmacological therapies.

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