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Plasma lipid profiles in relation to diabetic control in Nigerians

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Summary

Plasma lipid profiles — total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, triglycerides and phospholipids — were studied in relation to two parameters of diabetic control (fasting blood sugar (FBS) for short-term control and glycosylated haemoglobin (HBA_1C) for long-term control) in 46 diabetic patients (22 insulin-dependent (IDDM) and 24 non-insulin dependent (NIDDM)) and 22 non-diabetic control subjects. We confirmed the positive correlation between FBS and HBA_1C. All diabetic patients had significantly higher triglyceride levels ($P < 0.05$) than controls, which were not influenced by degree of glycaemic control. NIDDM patients tended to have higher than normal TC levels ($P < 0.05$). In IDDM, TC level was positively correlated with HBA_1C ($r = 0.37$, $P < 0.05$), and negative correlations were established between FBS and HDL-cholesterol ($r = -0.46$, $P < 0.02$) and the HDL-cholesterol : TC ratio ($r = -0.49$, $P < 0.01$), suggesting an increased atherogenic risk with poorer diabetic control.

It is concluded that lipoprotein abnormalities exist in Nigerian diabetics, though not as consistently as in Caucasians. The differences may be due to, among other factors, differences in genetic make-up, diet (typical African diet being rich in plant fibre and poor in cholesterogenic nutrients) and aetiology of the diabetic state (tropical diabetes being highly heterogeneous and now thought to be linked to malnutrition).

Résumé

Une étude des profils en lipides du plasma — cholestérol total, cholestérol-LDL, triglycérides et phospholipides — a été effectuée sur 22 diabétiques insulinodépendants (11 femmes et 11 hommes), 24 diabétiques non insulino-dépendants (12 femmes et 12 hommes) et 22 non-diabétiques (11 femmes et 11 hommes), en liaison avec deux paramètres de contrôle diabétique (taux de sucre dans le sang pris à jeun pour le contrôle à court terme et hémoglobine glycosylatée pour le contrôle à long terme). La corrélation positive entre les deux paramètres de contrôle a été confirmée. Tous les diabétiques présentaient des taux significativement plus élevés en triglycérides, non influencés par le degré de contrôle glycémique. Les malades non traités à l'insuline tendaient à avoir des taux de cholestérol total plus élevés que la normale. Chez ceux traités à l'insuline, les taux de cholestérol total s'élevaient avec l'augmentation de l'hémoglobine glycosylatée; de plus, chez cette catégorie de diabétiques, une corrélation négativement significative apparait entre les valeurs du taux de sucre dans le sang à jeun et celles du cholestérol-HDL, ainsi qu'avec le rapport cholestérol-HDL:cholestérol total suggérant ainsi un risque athérogénique accru en raisen d'une plus grande insuffisance du contrôle diabétique.

On en conclut que des anomalies en lipoprotéines existent chez les diabétiques nigérians, bien que d'une manière moins consistante que chez les individus d'origine caucasienne. Ceci peut être dû, entre autres facteurs, à des différences dans le patrimeine génétique, au régime alimentaire (le régime typique africain étant riche en fibres végétales et pauvre en substances nutritives cholestérogéniques) et à l'étiologie de l'état diabétique (le diabète tropical étant grandement hétérogène, et lié, comme on le pense actuellement, à la malnutrition).

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Introduction

Probably the most important long-term risk to the diabetic patient is vascular disease. There is overwhelming evidence in temperate countries that this excess risk is related to numerous lipid and lipoprotein abnormalities in diabetes, and that such abnormalities are even worse the poorer the degree of diabetic control. In tropical African developing countries like Nigeria, with increasingly available care for the acute hyper- and hypoglycaemic diabetic emergencies, ensuring longer life for diabetics, it is clear that such patients would be subject to this increased risk.

Although it is now recognized that diabetes in the tropics is heterogenous with a significant percentage being type III (malnutrition-related) [1], it is noted that a full characterization of this group of diabetics is still lacking. Moreover, the few studies available [2,3] have not examined lipid levels in either a cross-sectional or longitudinal fashion, or related these to atherothrombotic vascular risk. Such a study is crucial, especially in view of the empirical observations of reduced prevalence of vascular disease in diabetic and non-diabetic Africans compared to Caucasians [4,5]. This study attempts to address some of these issues.

Patients and methods

Patient characteristics

All diabetic subjects for this study attended the routine diabetic clinic at the University College Hospital, Ibadan between 1981 and 1984. The non-diabetic control subjects were low income hospital workers matched as much as possible for age, socio-economic status and sex with the diabetics. All hypertensive subjects (BP > 150/90 mmHg) were excluded from the study. Alcohol intake was minimal and in most cases restricted only to social occasions and none of them smoked. None of the subjects was on lipid-altering drugs including salicylates and oral contraceptive agents. The diabetic subjects were treated with insulin (insulin dependent, IDDM) or oral sulphonylureas or metformin (non-insulin dependent, NIDDM). Both forms of treatment were supplemented by dietary measures with varying degrees of compliance. All the diabetics were clinically stable and ambulant, with no clinically demonstrable retinopathy (on ophthalmoscopy), nephropathy (urinary albumin, serum creatinine), or macro-angiopathy (pedal pulses, ECG changes and absence of foot ulcers). All the subjects were studied after overnight fasting and the diabetic patients omitted their usual morning anti-diabetic drug.

Specimen collection

Fasting blood samples were obtained on each occasion from an antecubital vein without venostasis and collected into fluoride oxalate bottles for blood sugar analysis (Teklab, ML brand, Durham, U.K.) and heparinised tubes for glycosylated haemoglobin analysis (HBA_1C). Glucose assays were carried out on the same day while measurements of glycosylated haemoglobin and plasma lipids were done within 1 month of sample collection. For plasma lipids 6 ml of blood were collected into bottles containing Na_2EDTA (1 mg/ml), gently mixed and then placed on ice. Plasma was separated at 4°C within 1 h of collection. Separation of HDL from other lipoproteins was achieved by a precipitation method [6] using heparinmanganese chloride. The supernatant containing HDL was pipetted out and stored, as well as the remaining plasma, at −20°C until analysis.

Analytical determinations

Fasting blood sugar (FBS) was measured by the glucose oxidase method using 4-amino-phenazone as oxygen acceptor [7] and HBA_1C determined by a colorimetric method [8] with results expressed as fructose equivalents. Plasma triglyceride (TG) was measured by the method of Gottfried and Rosenberg [9], total cholesterol (TC) and HDL cholesterol (HDL-C) by a colour reaction described by Searcy and Berquist [10] and phospholipids by the method of King and Wooton [11]. For each assay, a commercial quality control (Well-control, Wellcome Reagents Ltd, Dartford, U.K.) and a pooled plasma sample of known value were always included.

The LDL-cholesterol (LDL-C) was derived from the following equation [12]:

$$\text{LDL-C} = \text{TC} - \left(\text{HDL-C} + \frac{\text{TG}}{5}\right).$$

Statistical methods

Results are presented as means ± s.e.m. Comparison between groups was performed using Student's *t*-test for unpaired data and Pearson's correlation coefficients. These statistical calculations were done on a microcomputer using the OXSTAT statistical package. The null hypothesis was rejected whenever $P < 0.05$.

Results

Patient characteristics

Table 1 shows that the subjects with NIDDM were, as expected, older ($P < 0.05$) and had greater body mass indices ($P < 0.05$) than those with IDDM. They also had lower FBS and HBA_1C values, probably reflecting the milder degree of their diabetes. Duration of diabetes was similarly shorter ($P < 0.05$) in the NIDDM group. There were significant positive correlations in non-diabetic subjects between age and levels of total cholesterol ($r = 0.53$, $P < 0.005$), HDL-cholesterol ($r = 0.48$, $P < 0.02$) and triglycerides ($r = 0.54$, $P < 0.01$). In IDDM, body mass index correlated positively with levels of HDL-cholesterol ($r = 0.39$, $P < 0.05$) and phospholipids ($r = 0.43$, $P < 0.03$), and LDL-cholesterol levels increased with increasing duration of diabetes ($r = 0.46$, $P < 0.02$). No significant correlations between these parameters were established in NIDDM.

Lipid profiles in different groups: relationship to glycaemic control

Fasting blood sugar and HBA_1C correlated positively as expected; the relationship is described by the regression equation:

$$HBA_1C = 111.6 + 3.6\ FBS$$
$$(n = 29,\ r = 0.43,\ P < 0.01).$$

Table 2 shows that total cholesterol levels in the diabetic subjects were higher than in the non-diabetic subjects, although that difference was significant only in IDDM ($P < 0.05$). Fasting triglyceride levels were higher in diabetes, whether IDDM or NIDDM ($P < 0.05$). In IDDM, FBS correlated negatively with HDL-cholesterol ($r = -0.6$, $P < 0.02$) and the HDL-cholesterol:total cholesterol ratio ($r = -0.49$, $P < 0.02$), while HBA_1C and total cholesterol correlated positively ($r = 0.37$, $P < 0.05$). In NIDDM, a weak relationship was established between FBS and fasting phospholipids ($r = 0.38$, $P < 0.05$).

Table 1. Clinical characteristics, duration of diabetes and blood glucose and glycosylated haemoglobin levels in the subjects

Physical and biochemical parameters	IDDM ($n = 22$, F = 11)	NIDDM ($n = 24$, F = 12)	All diabetics (IDDM + NIDDM) ($n = 46$, F = 23)	Non-diabetic controls ($n = 22$, F = 11)
Age (years)	42.6 ± 3.6	51.2 ± 2.3*†	46.9 ± 2.9*	36.5 ± 3.1
Body mass index (kg/m^2)	21.7 ± 0.8	24.6 ± 0.7*	23.1 ± 0.7	22.2 ± 1.0
Duration of diabetes (years)	5.6 ± 1.3	2.7 ± 0.5†	—	—
HBA_1C (μmol/l fructose)	195 ± 11.0*	156.8 ± 11.1*†	176.5 ± 11.0*	85.2 ± 4.1
FBS (mmol/l)	17.4 ± 1.71	9.9 ± 1.2	13.7 ± 1.4	4.1 ± 0.1

*$P < 0.05$ compared to non-diabetic subjects.
†$P < 0.05$ compared to IDDM.
F = female.
All values are means ± standard error of the mean.

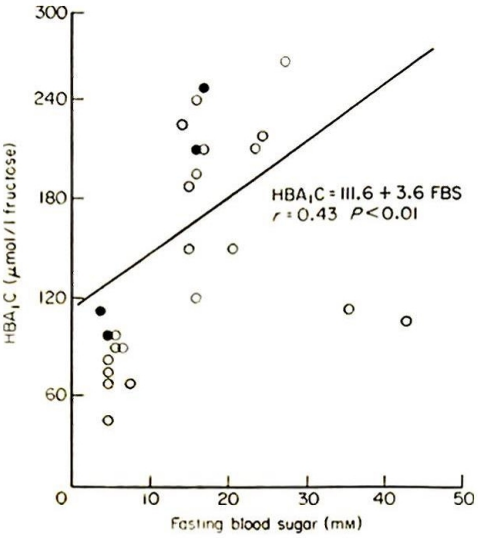

Fig. 1. Correlation between fasting blood sugar and glycosylated haemoglobin in normal and diabetic patients. (●) Indicates two or more coincident points. The line of best fit is shown.

Discussion

The finding of a positive correlation of age with total LDL-cholesterol and plasma triglyceride in non-diabetics but not in diabetics would probably explain the observation of the age-related susceptibility to atherosclerotic vascular disease in normal subjects and the lack of such in diabetics. The susceptibility to vascular disease in diabetics appears to be related more to the duration of their disease [13,14]. This trend is confirmed in this study, since in IDDM, LDL-cholesterol levels increased with increasing diabetic duration. As IDDM patients tend to be underweight generally, a relationship of body mass index with HDL-cholesterol (thought to be anti-atherogenic) may suggest that within limits increasing weight in this group of diabetics, itself an index of good glycaemic control, may protect against atherogenesis. That NIDDM patients tend to have higher total cholesterol levels than non-diabetics is hardly surprising, and may not be age-related, in view of the earlier demonstration of a lack of correlation of total cholesterol levels with age in this subgroup of diabetics. Similarly, the finding of elevated plasma triglyceride levels in all

Table 2. Plasma lipid levels in diabetic and control groups

Plasma lipids	IDDM (n = 22, F = 11)	NIDDM (n = 24, F = 12)	All diabetics (IDDM + NIDDM) (n = 46, F = 23)	Control (n = 22, F = 11)
Total cholesterol (mmol/l)	4.3 ± 0.3	4.3 ± 0.2*	4.3 ± 0.3	3.8 ± 0.2
HDL-cholesterol (mmol/l)	1.3 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
LDL-cholesterol (mmol/l)	2.2 ± 0.1	2.2 ± 0.2	2.2 ± 0.2	2.3 ± 0.1
HDL-cholesterol / Total cholesterol	0.32 ± 0.02	0.34 ± 0.02	0.33 ± 0.02	0.34 ± 0.01
Triglycerides (mmol/l)	1.2 ± 0.2*	1.5 ± 0.3*	1.3 ± 0.2**	0.7 ± 0.1
Phospholipids (g/l)	1.9 ± 0.1	1.9 ± 0.2	1.9 ± 0.2	1.6 ± 0.1

*$P < 0.05$; **$P < 0.02$, compared to control group.
F = female.
All values are means ± standard error of the mean.

diabetic groups is expected; the failure of such elevated levels to fall following improved glycaemic control, however, is surprising, and appears contrary to findings in Caucasian diabetics.

One explanation for this may be that in Nigerian diabetics, whose diet is usually non-cholesterogenic and mainly vegetable-fibre based, the major component of circulating plasma triglyceride is derived from hepatic processing of very low density lipoproteins (VLDL) rather than alimentarily processed prandial chylomicrons. This post-prandial chylomicron tide is more easily cleared by the endothelial-lining based insulin-sensitive lipoprotein lipase than VLDL.

Our findings suggest that, at least in IDDM, worsening control (FBS and HBA_1C levels) results in reduction of levels of HDL-cholesterol and ratio of HDL-cholesterol:total cholesterol. Thus, one may speculate that in this class of diabetics poor control means increased vascular risk. These observations were not made in NIDDM, probably suggesting that IDDM and NIDDM are different facets of a heterogeneous diabetic state. Alternatively, since NIDDM is usually associated with insulin resistance and hyper-insulinaemia, processing of plasma lipids is different. It also raises the question of whether, in NIDDM, risk of angiopathy is almost invariable, depending more on the presence of a 'diabetic' state rather than on how adequately the diabetic state is biochemically controlled.

There are very few comparable studies in African diabetics. Recently, Aduba *et al.* [2] reported that HDL-cholesterol and total cholesterol levels were higher in Nigerian diabetics compared to non-diabetic subjects. However, these workers failed to relate lipid levels to glycaemic control. However, in Caucasians numerous studies in juvenile onset diabetics [15–18] and NIDDM [19,20] demonstrate a significant positive correlation between worsening control and plasma levels of these atherogenic lipids, i.e. whilst in Caucasians plasma lipid profiles may be associated with atherosclerotic risk, such a conclusion is difficult to reach in Nigerians.

The reasons for this are probably manifold. One is the need to thoroughly re-classify many cases of diabetes seen in tropical developing countries, as there is now some evidence that aetiology in many cases is malnutrition-related [1]. Also, the traditional African diet, rich in vegetable fibre and relatively poor in saturated fat may prevent excessively high circulating lipid levels. However, the group we studied is homogenous in relation to socio-economic status and hence the role of diet in the observed differences may be minimal. Similarly, there is no sex bias, as our earlier work (Akanji and Agbedana, unpublished observations) has indicated that in this group of patients there is no sex-related difference in lipid profiles, especially when none of the women was on oral contraceptive therapy. Other sources of differences may be inherent genetic metabolic differences, longer duration of diabetes (usually) in Caucasians, and greater numbers of Caucasian diabetic groups studied.

We therefore conclude that lipid abnormalities exist in Nigerian diabetics but are not as consistent, especially in relation to glycaemic control, as levels in Caucasians [21]. Generally, worsening glycaemic control means a worsening plasma lipid pattern. Why differences exist in these two geographical groups of diabetics is not known but may be related to differences in the nature of the diabetic state, diet, genetic factors and duration of the disease.

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