Relation of Plasma Lipids to Insulin Resistance, Nonesterified Fatty Acid Levels, and Body Fat in Men From Three Ethnic Groups: Relevance to Variation in Risk of Diabetes and Coronary Disease

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Afro-Caribbean men in the United Kingdom have a favorable lipoprotein profile and are at low risk of coronary heart disease (CHD) compared with Europeans and South Asians, but are at high risk of non–insulin-dependent diabetes mellitus (NIDDM) compared with Europeans. To investigate these differences, a cross-sectional comparison was undertaken for measures of lipoprotein metabolism, body composition, and insulin's glucoregulatory and antilipolytic actions in 92 healthy men (42 to 61 years) of Afro-Caribbean, South Asian, or European origin. Afro-Caribbean men were more insulin-resistant than Europeans (insulin sensitivity [S_I], 1.96 *v* 3.01 $min^{-1} \cdot \mu U^{-1} \cdot mL$, $P < .01$). They nevertheless had a more favorable lipoprotein profile, with lower levels of very–low-density lipoprotein (VLDL) cholesterol (0.21 *v* 0.40 mmol/L, $P < .01$) and triglycerides (0.34 *v* 0.74 mmol/L, $P < .01$), lower serum total triglycerides, higher high-density lipoprotein 2 (HDL_2) cholesterol, and larger low-density lipoprotein (LDL) particle size. These differences were not accounted for by differences in nonesterified fatty acid (NEFA) levels, the sensitivity of suppression of NEFA levels to insulin, or body composition. South Asians were also more insulin-resistant than Europeans but had a less favorable lipoprotein profile. Afro-Caribbean men in the United Kingdom are as insulin-resistant as South Asian men but less susceptible to the lipid disturbances that characteristically accompany insulin resistance. This favorable lipid pattern may relate to more effective VLDL metabolism rather than a reduced supply of NEFA as substrate for triglyceride synthesis.

IN THE UNITED KINGDOM, Afro-Caribbean men have an increased prevalence of non–insulin-dependent diabetes mellitus (NIDDM) relative to Europeans, but a decreased incidence of coronary heart disease (CHD). With respect to South Asian (Pakistani and Indian) men in the United Kingdom, Afro-Caribbeans have a similar prevalence of NIDDM but, again, a reduced prevalence of CHD.[1-5] Given the well-established link between NIDDM and death from CHD, which is clearly seen in the South Asian group, the pattern of disease in Afro-Caribbeans appears paradoxical.

Insulin resistance is strongly associated with the development of NIDDM,[6] and in accordance with their increased risk of NIDDM, South Asians tend to be insulin-resistant compared with Europeans.[7] An increased insulin response to oral glucose, consistent with an increased prevalence of insulin resistance, has been reported in Afro-Caribbeans relative to Europeans.[8,9] However, in 2 studies,[8,10] the accompanying glucose level appeared to be reduced, suggesting that the additional insulin was effective in reducing glucose levels. The resolution of these uncertainties requires a direct measurement of insulin sensitivity. This has been undertaken in African-American men and women in the United States, who appear to be more insulin-resistant than white Americans,[11,12] but there have been no such studies in Afro-Caribbeans in the United Kingdom.

Differences among men of Afro-Caribbean, South Asian, and European origin in high-density lipoprotein (HDL) cholesterol and triglycerides have been reported, which accord with their relative risk for CHD mortality,[4,9,13] and these differences are also observed in comparisons between whites, and African-Americans. Among South Asians, HDL cholesterol levels are lower and triglycerides are higher compared with Europeans.[4] Low HDL cholesterol and high triglyceride levels are typically associated with insulin resistance.[14] The triglyceride and HDL cholesterol profile in South Asian men is therefore in accordance with their insulin resistance, but the profile in Afro-Caribbean men is not. Insulin resistance accompanied by a favorable lipid pattern in Afro-Caribbean men could account for the coexistence of a high NIDDM prevalence and low CHD incidence in this group, but its metabolic basis remains to be explained.

A possible resolution may lie in a dissociation of the sensitivities to the glucoregulatory and antilipolytic actions of insulin in Afro-Caribbeans. In Europeans and South Asians, these sensitivities could be closely correlated, but this might not be the case in Afro-Caribbeans. Since the supply of nonesterified fatty acid (NEFA) from lipolysis in fat cells largely determines the hepatic synthesis of very–low-density lipoprotein (VLDL) triglyceride, and plasma triglyceride levels, in turn, regulate HDL cholesterol and the low-density lipoprotein (LDL) subfraction pattern,[15] a relatively increased suppression of lipolysis by insulin in Afro-Caribbeans could have broadly favorable effects on the lipoprotein profile. A contributing factor to such differences could be a difference in body fat distribution, since South Asians and Europeans may have more central body fat than Afro-Caribbeans[4,9] and such fat has an intrinsically high lipolytic rate.[16] To further investigate the differing disease patterns and the metabolic associations observed in these 3 ethnic groups, we have evaluated the glucoregulatory and antilipolytic effects of insulin in a single study and examined the

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relationships of these measures to the lipid and lipoprotein profile and variation in body composition.

SUBJECTS AND METHODS

Design

A cross-sectional comparison of metabolic characteristics in Afro-Caribbeans, Europeans, and South Asians was undertaken. The study was limited to men because differences in the lipid and lipoprotein pattern among different ethnic groups are largest in men. Moreover, the mean body mass index (BMI) in the 3 ethnic groups is similar in men, whereas there are marked ethnic differences in the BMI among women. It was estimated that a sample size of 30 men in each group would be sufficient to detect a 23% lower insulin sensitivity among Afro-Caribbeans at 80% power and 5% significance compared with any other group.

Participants

Men aged 40 to 60 years were recruited from local family practices in northwest London. Potential recruits were identified from the family practitioner lists, and their records were checked to exclude individuals with obesity (BMI $\geq$ 30 kg $\cdot$ m^{-2}) or any condition (eg, diabetes, heart disease, and hypertension) or use of drugs likely to affect carbohydrate or lipid metabolism. In this way, 355 potential subjects were identified, and letters were sent in batches (alphabetical order) inviting them to participate. No further letters were sent once 30 persons in each group were studied. Ethnic origin was assigned on the basis of appearance and the parents' and grandparents' country of origin. Informed written consent was obtained in each case, and the study was approved by the local ethics committee.

Procedures

Each subject was instructed to eat more than 200 g/d carbohydrate for 3 days before testing to minimize dietary-induced differences in the pancreatic insulin response to glucose. They attended the Wynn Department metabolic day ward following a 12-hour overnight fast. Height and weight were measured and a general history was obtained, including details of exercise habits, tobacco and alcohol consumption, and family history of diabetes and heart disease. Blood pressure was recorded after 10 minutes of bed rest with the subject lying semirecumbent, after which cannulae were inserted into the antecubital veins of each arm, the cannula in the nondominant arm being used for blood sampling. Blood samples for measurement of fasting plasma glucose, insulin, and C-peptide (lithium-heparin anticoagulant) and serum lipid, lipoprotein, and apolipoprotein levels (plain tubes with granules to assist clot retraction) were taken through this cannula. Additional samples were taken for a second measurement of fasting glucose, insulin, C-peptide, and NEFA. Samples were placed on ice immediately and separated: for plasma, within 30 minutes, and for serum, after 60 minutes had elapsed for clot formation and retraction. Following the fasting sampling, an intravenous glucose injection (0.5 g/kg body weight as 50% dextrose solution) was administered over 3 minutes via the opposite cannula, which was then removed. Samples for measurement of glucose, insulin, C-peptide, and NEFA were taken at 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 minutes following commencement of the injection. A further sample was taken at 180 minutes for measurement of serum triglycerides. Upon completion of the intravenous glucose tolerance test (IVGTT), the total fat and lean mass and regional body fat mass were measured by dual-energy x-ray absorptiometry (DXA) using a Lunar DPX-L scanner (Lunar, Madison, WI).

Laboratory Measurements

Plasma glucose was determined within 24 hours on samples stored at −4°C using a glucose oxidase method.[17] Plasma insulin and C-peptide levels were measured in batches on samples stored at −20°C by double-antibody radioimmunoassay with materials supplied by Guildhay (Surrey, UK). Within- and between-batch coefficients of variation were 2% to 3% (glucose), 4% to 6% (insulin), and 7% to 9% (C-peptide). Serum NEFA levels were measured by enzymatic assay (WAKO NEFA-C kit; Alpha Laboratories, Eastleigh, UK). Serum total cholesterol and triglyceride levels were measured by fully enzymatic methods. HDL cholesterol and HDL_3 cholesterol were determined after sequential precipitation with heparin and manganese ions[18] and dextran sulfate,[19] respectively. HDL_2 cholesterol was calculated as the difference between HDL and HDL_3 cholesterol. VLDL cholesterol and triglyceride levels were measured after preparative ultracentrifugation at a solvent density of 1.006 g/L. LDL was calculated as the difference between total cholesterol and the sum of HDL and VLDL cholesterol. Apolipoproteins AI, AII, and B were determined by immunoturbidimetry,[20] and lipoprotein(a) was determined by an enzyme-linked immunosorbent assay (Biopool, Umea, Sweden). Modal LDL particle size was assessed by gradient gel electrophoresis using a Pharmacia GE 2/4 LS cell to analyze samples on precast 3% to 13% gels (Gradipore, Sydney, Australia). Following staining with Sudan black B, the gels were scanned with a laser desitometer (Personal Densitometer; Molecular Dynamics, Sunnyvale, CA). LDL particle size was assessed using a pooled serum standard containing particles of known size, kindly provided and calibrated by Professor R.M. Krauss, University of California, Berkley.

Data Analysis

DXA-derived regional fat mass in the subscapular, waist, hip, and thigh regions was defined with reference to anatomical bone landmarks as previously described.[21] Android fat was estimated as the sum of fat in the subscapular and waist regions, and gynoid fat as the sum of fat in the hip and thigh regions. The android to gynoid fat mass ratio was calculated.

Mean fasting plasma glucose, insulin, C-peptide, and NEFA levels were derived from the 2 basal measurements, and IVGTT incremental glucose, insulin, and C-peptide areas (ie, area between the fasting level and the IVGTT concentration profile) were calculated by the trapezoidal rule (ie, the sum of all areas consisting of time interval multiplied by the average of the concentrations at the beginning and end of that time interval). Measures of insulin sensitivity, secretion, and elimination were derived by mathematical modeling analysis of the IVGTT glucose, insulin, and C-peptide concentration profiles, using programs written in Fortran 77. Insulin sensitivity (S_i) and glucose effectiveness (S_g) were determined using the minimal model of glucose disappearance.[22] The relatively high glucose dose (0.5 g/kg) we use provides for a sufficient endogenous insulin response in nondiabetics without recourse to additional augmentation of pancreatic insulin secretion. This is apparent in the high rate of model identification and good correlation with measures of insulin sensitivity derived from the euglycemic clamp ($r = .92$) that we obtain.[23,24] Insulin delivery characteristics were evaluated using the minimal model of posthepatic insulin delivery,[25] which provides measures of the fractional insulin elimination rate and the responsiveness of first- and second-phase posthepatic insulin delivery to glucose, ϕ_1 and ϕ_2, respectively. A combined model of insulin and C-peptide delivery[26,27] was used to quantify the fractional insulin and C-peptide elimination rate, a measure of the fraction of newly secreted insulin that passes out of the liver, and basal and incremental insulin secretion during the IVGTT, in total and during first- and second-phase secretion. The models describing insulin delivery have been evaluated previously in animals and humans.[23,26,28]

The decline in NEFA concentrations during the IVGTT was quantified in terms of the rate constant for the NEFA decay profile. This was calculated in each individual as the slope of the regression line passing through the logarithmic NEFA concentrations during the exponential decay phase, which generally occurred between 30 and 120 minutes.

Since the rate of decay of NEFA concentrations depends on the accompanying insulin concentration, the NEFA decay rate was standardized in each individual by dividing by the accompanying increment in the insulin concentration to provide a NEFA suppression index (minutes per microunit per milliliter, multiplied by -1×10^6 to provide a measure that increases with increasing sensitivity). Preliminary to the present analysis, the behavior of this index was explored in 3 groups of 30 men of European origin as previously described.[29] NEFA suppression indices in groups selected to represent upper, middle, and lower quintiles of S_i were (mean ± SD) 5.87 ± 3.64, 3.42 ± 2.21, and 1.68 ± 1.38, respectively (I.F. Godsland, unpublished data, March 1995). The change in triglyceride concentrations during the course of the IVGTT was estimated as the triglyceride concentration at 180 minutes minus the fasting triglyceride concentration.

Statistical analyses were performed using the SYSTAT statistical package (SYSTAT, Evanston, IL). Significant differences among the 3 groups were identified by ANOVA, and where significant differences were found, pairwise comparisons were made with the Tukey HSD post hoc test. Differences between categorical variables were assessed by the Spearman chi-square test. Pairwise comparisons between variables measured at different time points during the IVGTT within each group were made by Student's *t* test. Relationships between variables were explored using Pearson correlation analysis. Differences between groups independent of age were explored by analysis of covariance. For variables that showed nonparallel slopes with age across the 3 groups, comparisons were made between data standardized to the mean age of the entire study group. Multiple linear regression analysis was used to explore predictors of variables that differed significantly between the different ethnic groups. In these analyses, dummy variables were assigned to South Asian and Afro-Caribbean ethnic groups.

RESULTS

Afro-Caribbean and European men were of similar age, but South Asian men were significantly younger than the other groups (Table 1). Afro-Caribbean men had a significantly lower frequency for the family history of heart disease compared with Europeans or South Asians. Each group differed from the others in lean body mass in the order (from highest to lowest) of Afro-Caribbean, European, and South Asian. Central adiposity, measured by the android to gynoid fat mass ratio, was lowest in Afro-Caribbeans. Otherwise, there were no differences in demographic, anthropometric, or blood pressure variables. Afro-Caribbeans had the lowest mean triglyceride level, which was significantly different versus South Asians (Table 2). VLDL triglyceride and cholesterol levels were significantly lower in Afro-Caribbeans versus both of the other groups. There was a borderline significant variation in HDL_2 cholesterol levels, with Afro-Caribbeans having the highest mean concentrations. Afro-Caribbeans had the highest mean LDL particle size and lipoprotein(a) concentration. South Asians had the highest mean fasting insulin and C-peptide concentrations, with the difference being significant versus the Europeans for insulin and versus both Afro-Caribbeans and Europeans for C-peptide.

The IVGTT insulin response was greater in both Afro-Caribbeans and South Asians in comparison to Europeans, and this was also the case for the IVGTT C-peptide response and phase 1 pancreatic insulin secretion in the South Asians (Table 3). Phase 2 posthepatic insulin delivery (ϕ_2) was higher in South Asians versus Europeans (results not shown). There were no significant differences in phase 1 posthepatic insulin delivery (ϕ_1) and the insulin elimination rate derived from the posthepatic insulin delivery model, or in the hepatic insulin throughput index, insulin elimination rate, or C-peptide elimination rate derived from the pancreatic secretion model (results not shown). Insulin sensitivity differed among groups, being 35% and 36% lower in Afro-Caribbeans and South Asians, respectively, compared with Europeans ($P = .09$ and .07 on post hoc pairwise testing, respectively). The mean IVGTT NEFA concentration profiles are shown in Fig 1. There was an initial increase in NEFA that reached a maximum at 30 minutes in each group, after which NEFA decreased to a minimum at 120 minutes and then began to increase again. Mean NEFA concentrations were significantly higher in South Asians compared with both Afro-Caribbeans and Europeans at the maximum of 30 minutes, but did not differ at the minimum of 120 minutes (Table 3). The NEFA decay rate was highest in South Asians ($P = .051$ *v* Europeans), but after standardization for the accompanying variation in insulin levels by derivation of the NEFA suppression index, there was no longer a significant variation between

Table 1. Demographic, Anthropometric, and Blood Pressure Characteristics in Three Ethnic Groups

Characteristic	Afro-Caribbeans (n = 30)	South Asians (n = 31)	Europeans (n = 31)	Significance (ANOVA/chi-square)
Age (yr)	53.7 ± 4.5	48.5 ± 4.3*	53.8 ± 3.5	<.001
BMI (kg/m²)	26.9 ± 4.1	25.3 ± 3.0	26.3 ± 3.8	NS
Smoking, % (never/previous/current)	67/13/20	61/17/22	52/29/19	NS
Alcohol consumption, % (0/1-15/>15 U/wk)	43/57/0	42/52/6	39/42/19	NS
Exercise, % (none/nonaerobic/aerobic)	33/67/0	23/74/3	48/52/0	NS
Family history of diabetes (%)	10.0	16.1	9.6	NS
Family history of heart disease (%)	3.3	19.4‡	29.0‡	<.01
Lean body mass (kg)	58.1 ± 6.7†	47.3 ± 6.2†	53.6 ± 4.9†	<.001
Total fat mass (kg)	18.8 ± 8.7	20.9 ± 6.7	20.9 ± 6.7	NS
Android fat mass (kg)	6.66 ± 3.20	7.79 ± 2.53	7.74 ± 3.11	NS
Gynoid fat mass (kg)	5.48 ± 2.53	5.75 ± 1.97	6.07 ± 2.66	NS
Android/gynoid ratio	1.20 ± 0.19	1.37 ± 0.20‡	1.30 ± 0.25	<.05
Systolic blood pressure (mm Hg)	128.7 ± 19.3	124.1 ± 14.2	125.0 ± 16.1	NS
Diastolic blood pressure (mm Hg)	83.2 ± 10.2	81.5 ± 12.2	80.4 ± 11.1	NS

NOTE. Results are the mean ± SD.

*Significantly different *v* Afro-Caribbeans and Europeans.

†Significantly different *v* each of the other 2 groups.

‡Significantly different *v* Afro-Caribbeans.

Table 2. Fasting Serum Lipid, Lipoprotein, and Apolipoprotein and Plasma Glucose, Insulin, and C-Peptide Concentrations in Three Ethnic Groups (mean ± SD)

Characteristic	Afro-Caribbeans (n = 30)	South Asians (n = 31)	Europeans (n = 31)	Significance (ANOVA)
Cholesterol (mmol/L)	4.82 ± 1.15	5.23 ± 1.03	5.40 ± 0.97	NS
Triglycerides (mmol/L)‡	0.96, 0.61-1.50*	1.59, 0.91-2.77	1.26, 0.64-2.48	<.01
LDL cholesterol (mmol/l)	3.24 ± 1.14	3.34 ± 0.81	3.49 ± 0.83	NS
HDL cholesterol (mmol/L)	1.35 ± 0.28	1.24 ± 0.32	1.32 ± 0.33	NS
HDL_2 cholesterol (mmol/L)	0.53 ± 0.23	0.39 ± 0.19	0.48 ± 0.26	.052
HDL_3 cholesterol (mmol/L)	0.81 ± 0.11	0.85 ± 0.19	0.84 ± 0.16	NS
VLDL triglyceride (mmol/L)‡	0.34, 0.14-0.84†	0.92, 0.41-2.03	0.74, 0.30-1.84	<.001
VLDL cholesterol (mmol/L)‡	0.21, 0.09-0.47†	0.51, 0.23-1.11	0.40, 0.16-0.98	<.001
Apolipoprotein B (g/L)	73.2 ± 25.6	79.8 ± 19.3	83.5 ± 17.5	NS
Apolipoprotein AI (g/L)	121.1 ± 16.5	117.5 ± 20.8	128.0 ± 19.7	NS
Apolipoprotein AII (g/L)	37.7 ± 5.6	38.4 ± 7.4	40.8 ± 7.4	NS
Apolipoprotein(a) (g/L)‡	26.4, 11.6-64.6†	12.0, 6.1-27.6	9.1, 2.9-35.6	<.001
LDL particle size (nm)	264.5 ± 11.2*	255.6 ± 13.6	260.3 ± 10.9	<.05
NEFA (mEq/L)‡	0.62, 0.43-0.89	0.71, 0.54-0.94	0.61, 0.40-0.93	NS
Glucose (mmol/L)	5.35 ± 0.78	5.40 ± 0.58	5.30 ± 0.44	NS
Insulin (pmol/L)‡	42.3, 20.5-88.8	65.2, 36.9-116.6	38.5, 17.3-85.7*	<.01*
C-peptide (pmol/L)§	482, 310-690*	647, 449-878	501, 297-759*	<.01

*Significantly different *v* South Asians.

†Significantly different *v* South Asians and Europeans.

‡Geometric means with back-transformed negative and positive standard deviation limits.

§Square of the mean of square-root–transformed data, with back-transformed negative and positive standard deviation limits.

the groups. South Asians showed a net increase in triglyceride levels during the IVGTT, which was significant compared with the observed change in the other 2 groups. Triglyceride concentrations at the end of the IVGTT were significantly higher in South Asians ($P < .01$) and significantly lower in Afro-Caribbeans ($P < .01$) compared with pre-IVGTT levels.

After adjusting for age, ANOVA across groups for total fat, android fat, total cholesterol, and incremental pancreatic insulin secretion showed significant variation (all $P < .05$), but the variation was no longer significant for HDL_2 cholesterol ($P = .08$), phase 2 posthepatic insulin delivery (ϕ_2, $P = .09$), or phase 1 pancreatic insulin secretion ($P = .06$). In a post hoc pairwise comparison of age-standardized variables showing significant variation on ANOVA, the difference between Afro-Caribbeans and South Asians in the IVGTT C-peptide response became significant ($P < .01$), as did the differences in insulin sensitivity between Afro-Caribbeans and South Asians compared with Europeans (both $P < .01$).

The strongest correlations between measures of NEFA metabolism and other metabolic and body composition variables

Table 3. IVGTT-Derived Measures (mean ± SD)

Characteristic	Afro-Caribbeans (n = 30)	South Asians (n = 31)	Europeans (n = 31)	Significance (ANOVA)
Incremental area				
Glucose (mmol/L · min)	560 ± 224	500 ± 156	532 ± 191	NS
Insulin (pmol/L · min × 10^{-3})‡	25.3, 15.2-42.2*	33.0, 18.2-59.7*	17.1, 9.7-30.4	<.001
C-peptide (pmol/L · min × 10^{-3})‡	131, 93-183	170, 115-250*	119, 72-199	<.01
Minimal model of glucose disappearance				
Insulin sensitivity, S_I ($min^{-1} \cdot \mu U^{-1} \cdot mL$)§	1.96, 0.62-4.05	1.92, 0.77-3.59	3.01, 1.22-5.58	<.05
Glucose effectiveness, S_g (min^{-1})‡	1.39, 0.78-2.49	1.44, 0.78-2.65	1.35, 0.74-2.46	NS
Pancreatic secretion model				
Incremental pancreatic insulin secretion (pmol/mL)‡	3.33, 1.87-5.96	4.54, 2.10-9.79	3.05, 1.44-6.43	NS
Phase 1 pancreatic insulin secretion (pmol/mL)	1.13 ± 0.60	1.32 ± 0.88*	0.80 ± 0.41	<.01
Phase 2 pancreatic insulin secretion (pmol/mL)§	2.24, 0.06-5.92	4.16, 0.36-10.82	2.81, 0.25-6.21	NS
NEFA and triglyceride measures				
NEFA at 30 min (mmol/L)‡	0.77, 0.38-1.57†	1.20, 0.59-2.45	0.69, 0.34-1.42†	<.01
NEFA at 120 min (mmol/L)‡	0.28, 0.11-0.69	0.27, 0.11-0.67	0.30, 0.12-0.75	NS
NEFA decay rate, 30-120 min (min^{-1} × 10^3)	−4.52 ± 3.96	−6.43 ± 4.69	−3.84 ± 3.61	<.05
NEFA suppression index ($min^{-1} \cdot \mu U^{-1} \cdot mL \times -10^6$)	2.14 ± 2.36	2.59 ± 4.97	3.21 ± 7.40	NS
Triglycerides at 180 min (mmol/L)‡	0.87, 0.53-1.45†	1.81, 1.00-3.25	1.24, 0.60-2.58	<.001
Delta triglyceride, fasting to 180 min (mmol/L)	−0.065 ± 0.225†	0.264 ± 0.368	0.012 ± 0.319†	<.001

*Significantly different *v* Europeans.

†Significantly different *v* South Asians.

‡Geometric means with back-transformed negative and positive standard deviation limits.

§Square of the mean of square-root–transformed data, with back-transformed negative and positive standard deviation limits.

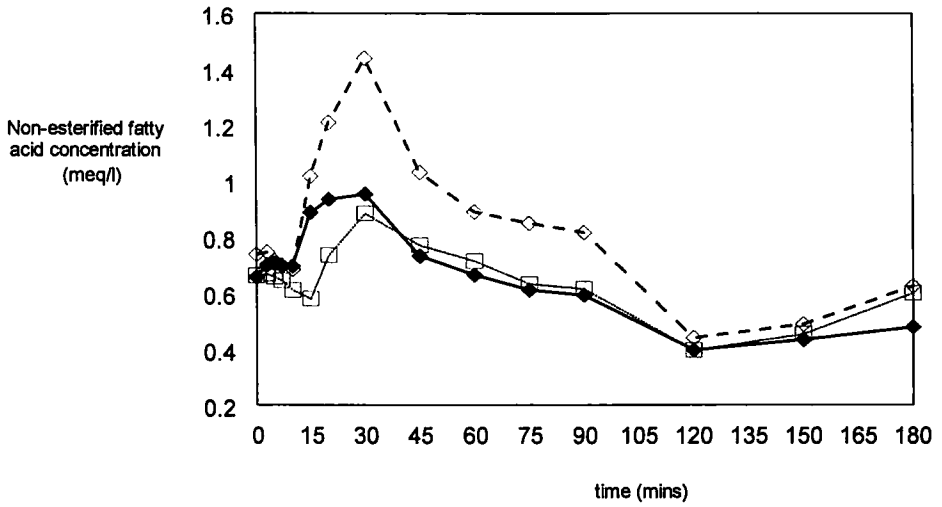

Fig 1. Mean NEFA profile during IVGTT in Afro-Caribbeans (n = 30, ◆), South Asians (n = 31, ◇), and Europeans (n = 31, □).

were obtained with the IVGTT NEFA concentration at 30 minutes. There were significant positive correlations between this measure and VLDL cholesterol in all groups ($r = .42$ to .47, $P < .05$), and with triglycerides in South Asians ($r = .64$, $P < .001$) and Afro-Caribbeans ($r = .46$, $P < .05$). The strong correlation between the IVGTT NEFA concentration at 30 minutes and triglycerides in the South Asians extended to LDL particle size ($r = .60$, $P < .01$) and HDL_2 cholesterol ($r = .46$, $P < .05$). In contrast, South Asians exhibited no correlation between the IVGTT NEFA concentration at 30 minutes and android fat mass. Europeans and South Asians, on the other hand, showed no significant associations between the IVGTT NEFA concentration at 30 minutes and LDL particle size or HDL_2 cholesterol, but showed significant associations between the IVGTT NEFA concentration at 30 minutes and android fat mass ($r = .38$ to .45, $P < .05$). There were no significant correlations between the IVGTT NEFA concentration at 30 minutes and the lean body mass, change in triglyceride concentration during the IVGTT, measures of insulin concentration (with the exception of a positive correlation with basal insulin in South Asians) and insulin sensitivity, and android to gynoid fat mass ratio. The correlations with total and gynoid fat mass resembled those found with android fat mass but were slightly weaker. The change in triglyceride concentrations during the IVGTT correlated positively with the IVGTT insulin incremental area in South Asians ($r = .41$, $P < .05$) and Afro-Caribbeans ($r = .46$, $P < .05$).

Univariate correlations for the interrelated metabolic variables of triglyceride, HDL, and insulin metabolism and body composition for the Afro-Caribbean group are shown in Table 4. Extensive intercorrelations were apparent and similar patterns of association were also found in the South Asian and European groups (results not shown). Relationships between the triglyceride concentration and insulin sensitivity in each group are illustrated in Fig 2.

Predictors of VLDL cholesterol, HDL_2 cholesterol, and LDL particle size in multiple linear regression analysis are shown in Table 5. The predictors of VLDL cholesterol that were entered

Table 4. Pearson Correlation Coefficients for Metabolic Variables of the Insulin Resistance Syndrome and Measures of Body Composition in Afro-Caribbeans

	Triglycerides	VLDL Cholesterol	LDL Particle Size	HDL_2 Cholesterol	Basal Insulin	IVGTT Insulin	Insulin Sensitivity	Total Lean Tissue	Total Body Fat	Android Fat Mass	Gynoid Fat Mass	Android/ Gynoid Ratio
Triglycerides	1.00											
VLDL cholesterol	.86‡	1.00										
LDL particle size	−.54†	−.39*	1.00									
HDL_2 cholesterol	−.43*	−.32	.59†	1.00								
Basal insulin	.35	.31	−.40*	−.59†	1.00							
IVGTT insulin	.46*	.25	−.52†	−.51†	.62‡	1.00						
Insulin sensitivity	−.41*	−.25	.34	.47*	−.50†	−.65‡	1.00					
Total lean tissue	.31	.37*	−.28	.03	.37*	.36*	−.15	1.00				
Total body fat	.44*	.21	−.40*	−.47*	.51†	.67‡	−.57†	.45*	1.00			
Android fat mass	.47*	.22	−.44*	−.50†	.52†	.69‡	−.61‡	.43*	.99‡	1.00		
Gynoid fat mass	.42*	.22	−.34	−.43*	.49†	.63‡	−.53†	.48†	.98‡	.96‡	1.00	
Android/gynoid ratio	.30	.05	−.47*	−.46*	.26	.40*	−.46*	−.07	.29	.39*	.15	1.00

NOTE. Data were transformed as described in Tables 1-3.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

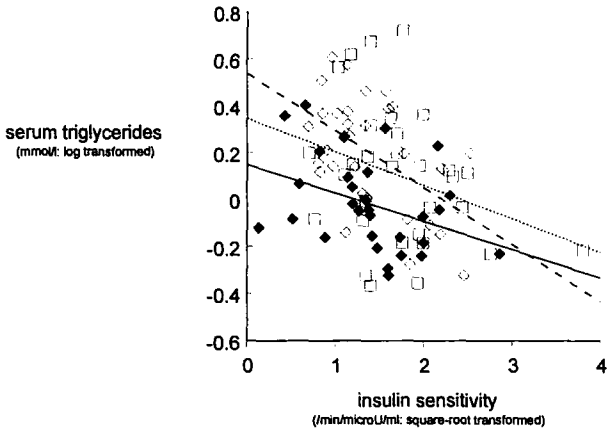

Fig 2. Regression line for fasting serum triglycerides versus insulin sensitivity in Afro-Caribbeans (n = 30, ◆), South Asians (n = 31, ◇), and Europeans (n = 31, □).

into the regression model as independent variables were age, total lean body mass, android and gynoid fat mass, IVGTT insulin response, insulin sensitivity, IVGTT 30-minute NEFA concentration, and South Asian or Afro-Caribbean ethnic group. The same predictors were used in the analysis of HDL_2 cholesterol and LDL particle size, except that the IVGTT 30-minute NEFA concentration was replaced by VLDL cholesterol. The rationale for this is that, metabolically, NEFA levels would most likely influence HDL_2 cholesterol and LDL particle size via VLDL metabolism. The only significant predictors of VLDL cholesterol were the 30-minute IVGTT NEFA concentration (positive) and Afro-Caribbean ethnicity (negative). The only significant predictor of HDL_2 cholesterol and LDL particle size in each analysis was VLDL cholesterol.

DISCUSSION

An increase in plasma triglycerides leads to the triglyceride enrichment of lipoproteins, exchange of cholesterol and triglycerides between triglyceride-rich lipoproteins and HDL, and preferential formation of potentially atherogenic small, dense LDL particles.[30] Elevated triglyceride, low HDL cholesterol, especially the HDL_2 subfraction, and small, dense LDL particles form a cluster of intercorrelated lipid disturbances associated with the insulin resistance syndrome.[31] These disturbances are linked with increased adiposity, particularly in the central area of the body.

Table 5. Predictors of VLDL Cholesterol, LDL Particle Size, and HDL_2 Cholesterol in Multiple Linear Regression Analysis

Predictor	VLDL Cholesterol	LDL Particle Size	HDL_2 Cholesterol
Age	−.10	.15	.11
Total body lean mass	.21	−.12	.11
Android fat mass	.49	−.13	−.48
Gynoid fat mass	−.37	.27	.30
IVGTT insulin response	.17	−.19	−.12
Insulin sensitivity	.04	−.02	.14
South Asian ethnicity	−.04	.02	.08
Afro-Caribbean ethnicity	−.44†	.09	−.01
30-min IVGTT NEFA concentration	.27*	—	—
VLDL cholesterol	—	−.49†	−.30*

NOTE. Transformations were applied as in Tables 1-3. Standardized regression coefficients and significance levels are shown. Where no significance is given, the association was nonsignificant. Dummy variables were assigned for South Asian and Afro-Caribbean ethnicity.
*$P < .01$.
†$P < .001$.

The previous observation that Afro-Caribbean men in the United Kingdom have relatively low triglyceride and high HDL levels despite having the elevated insulin levels typical of insulin resistance was unexpected, albeit consistent with the low incidence of CHD and high incidence of NIDDM in this group. In the present study, we have confirmed that men of Afro-Caribbean origin are indeed insulin-resistant compared with men of European origin, and their insulin resistance is comparable to that of men in the well-characterized South Asian group. Nevertheless, triglyceride and VLDL cholesterol and triglyceride levels were lower in Afro-Caribbeans than in South Asians, HDL_2 cholesterol concentrations were higher, LDL particles tended to be larger, and total and android fat masses were smaller. This suggests a dissociation in Afro-Caribbeans between the typical patterns of association found for insulin sensitivity, triglyceride metabolism, and body fat distribution. However, this was found not to be the case, since Afro-Caribbeans exhibited univariate interrelationships between these variables typical of those previously reported in other groups (similar relationships have been reported previously in diabetic African-American men[32]). Thus, in Afro-Caribbeans, the typical pattern of metabolic associations with insulin sensitivity was present but superimposed on a background of comparatively favorable triglyceride metabolism (Fig 2). There is a negative association between insulin sensitivity and triglycerides in all 3 groups despite the coexistence of comparatively low insulin sensitivity and low triglycerides in the Afro-Caribbean group. However, it is apparent that among Afro-Caribbean men the regression line is displaced to lower levels of triglycerides. Therefore, the familiar associations between insulin sensitivity and triglycerides are as apparent in Afro-Caribbeans as in Europeans or South Asians, but they are present at lower levels of triglycerides overall.

One of the principal determinants of the rate of triglyceride synthesis is the supply of NEFA to the liver. The principal source of NEFA is adipose tissue lipolysis, and an important controlling factor in adipose tissue lipolysis is its suppression by insulin. Insulin resistance may extend to this suppression such that, in insulin-resistant states, there is less effective suppression of lipolysis by insulin and, consequently, more triglyceride synthesis.[15] This could then contribute to the positive association between high triglyceride levels and hyperinsulinemia found in the insulin resistance syndrome. To account for the coexistence of relatively low glucoregulatory insulin sensitivity and low triglyceride levels in Afro-Caribbeans, we hypothesized that the suppression of lipolysis might be more sensitive to insulin in Afro-Caribbeans than in other groups. However, we found that the degree of NEFA suppression was identical in Afro-Caribbeans and Europeans and the rate of decay, standardized for the accompanying insulin concentration, did not differ significantly between these groups.

An alternative explanation for the low triglyceride levels in Afro-Caribbeans might be found in the variation in body fat

distribution. Centrally located body fat is one of the principal sources of NEFA for hepatic triglyceride synthesis,[16] and in the present study, Afro-Caribbeans were found to have the lowest android fat mass. Android fat mass was positively related to the IVGTT 30-minute NEFA concentration in the Afro-Caribbean group, and to fasting triglyceride levels. Moreover, in both univariate and multivariate analysis, the IVGTT 30-minute NEFA concentration was positively related to fasting VLDL cholesterol levels. This initial increase in NEFA concentrations following intravenous glucose injection has not been reported previously and may be caused by catecholamine release. To the extent that basal NEFA flux determines basal triglyceride levels, the correlations with android fat mass and fasting triglycerides suggest that the IVGTT 30-minute NEFA concentration might provide an index of basal NEFA flux from central fat depots to the liver. However, the IVGTT 30-minute NEFA concentration did not differ between Afro-Caribbeans and Europeans, and in multivariate analysis, android fat mass did not independently predict VLDL cholesterol levels. It is therefore unlikely that a smaller android fat mass can account for the lower triglyceride levels in the Afro-Caribbean group.

These observations, as well as the independent association in multivariate analysis between Afro-Caribbean ethnicity and a low VLDL cholesterol level, suggest that Afro-Caribbeans have a mechanism for maintaining low VLDL triglyceride and cholesterol that is independent of any of the variables evaluated here. A further possibility, then, is that the low levels of VLDL triglyceride and VLDL cholesterol result from a faster clearance of VLDL by lipoprotein lipase. VLDL triglyceride and VLDL cholesterol are inversely correlated with postheparin lipoprotein lipase activity.[33] In this respect, it is noteworthy that almost all of the lower triglyceride levels in Afro-Caribbeans could be accounted for by lower triglycerides in the VLDL fraction. Moreover, triglyceride levels decreased after glucose challenge in Afro-Caribbeans, in contrast to the increase in the equally insulin-resistant South Asian group. This elevation of triglyceride levels has been previously demonstrated in South Asians following oral glucose[4] and in insulin-resistant Europeans following intravenous glucose.[29] The mechanism underlying this increase is unknown, but it is noteworthy that, in accordance with our previous observations in insulin-resistant Europeans,[29] there was a positive correlation between the change in triglyceride concentrations and change in insulin concentrations during the IVGTT in both South Asians and Afro-Caribbeans. The net decrease, rather than increase, of triglycerides in Afro-Caribbeans is then further evidence for an additional characteristic tending to counter the effects of their relative insulin resistance on triglyceride metabolism. The resolution of these differences will require further comparative studies of factors involved in triglyceride elimination, for example, postprandial triglyceride metabolism and lipase activities. In this respect, postheparin plasma hepatic lipase activities have been reported to be about 40% lower in African-American men compared with whites, and this difference is associated with a genetic polymorphism in the 5′ flanking region of the hepatic lipase gene (*LIPC* genotype).[34] This polymorphism appears to render hepatic lipase activity in men less susceptible to the increase that occurs at puberty in response to increasing androgen levels. It appears to be about 3 times more common in African-American men compared with white American men and is associated with significantly higher HDL concentrations. However, it seems likely that other factors are involved, since when African-American and white American men with the same *LIPC* genotype were compared, hepatic lipase activities were still significantly lower in African-Americans. Moreover, in the present study, the principal difference between Afro-Caribbean and European men laid in VLDL rather than HDL, the converse of the differences reported in studies of the *LIPC* genotype.

In conclusion, Afro-Caribbeans in the United Kingdom tend to be insulin-resistant, in accordance with their increased risk of diabetes, and exhibit the metabolic correlations typically found with variation in insulin sensitivity. However, these associations were present against a background of low triglyceride and VLDL concentrations. Decreased triglyceride production as a result of an increased sensitivity of the suppression of adipose tissue lipolysis to insulin or a decreased android fat mass did not appear to be responsible for these low levels. Several observations were consistent with more effective triglyceride metabolism in Afro-Caribbeans, including higher HDL_2 cholesterol and larger LDL particle size and a significant decrease in triglyceride concentrations during the IVGTT. A more rapid clearance of triglyceride-rich lipoproteins independently of insulin sensitivity in Afro-Caribbeans could then be responsible for their reduced incidence of CHD. Further studies will be needed to confirm this possibility.

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