The Atherogenic Lipoprotein Profile Associated With Obesity and Insulin Resistance Is Largely Attributable to Intra-Abdominal Fat

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Obesity and insulin resistance are both associated with an atherogenic lipoprotein profile. We examined the effect of insulin sensitivity and central adiposity on lipoproteins in 196 individuals (75 men and 121 women) with an average age of 52.7 years. Subjects were subdivided into three groups based on BMI and their insulin sensitivity index (S_I): lean insulin sensitive (n = 65), lean insulin resistant (n = 73), and obese insulin resistant (n = 58). This categorization revealed that both obesity and insulin resistance determined the lipoprotein profile. In addition, the insulin-resistant groups had increased central adiposity. Increasing intra-abdominal fat (IAF) area, quantified by computed tomography scan and decreasing S_I, were important determinants of an atherogenic profile, marked by increased triglycerides, LDL cholesterol, and apolipoprotein B and decreased HDL cholesterol and LDL buoyancy (Rf). Density gradient ultracentrifugation (DGUC) revealed that in subjects who had more IAF and were more insulin resistant, the cholesterol content was increased in VLDL, intermediate-density lipoprotein (IDL), and dense LDL fractions whereas it was reduced in HDL fractions. Multiple linear regression analysis of the relation between the cholesterol content of each DGUC fraction as the dependent variable and IAF and S_I as independent variables revealed that the cholesterol concentration in the fractions corresponding to VLDL, IDL, dense LDL, and HDL was associated with IAF, and that S_I additionally contributed independently to VLDL, but not to IDL, LDL, or HDL. Thus an atherogenic lipoprotein profile appears to be the result primarily of an increase in IAF, perhaps via insulin resistance. ***Diabetes*** **52:172–179, 2003**

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CT, computed tomography; DGUC, density gradient ultracentrifugation; IAF, intra-abdominal fat; IDL, intermediate-density lipoprotein; LIR, lean insulin resistant; LIS, lean insulin sensitive; OIR, obese insulin resistant; Rf, LDL relative flotation; SCF, subcutaneous fat; S_I, insulin sensitivity index; WHR, waist-to-hip ratio.

Obesity has been clearly demonstrated to be associated with insulin resistance (1–4). Insulin resistance in turn has been found to be linked with many of the conditions typically associated with obesity (5–7) and other conditions that appear to be less typically associated with simple obesity (8). These effects have generally been observed across sex (9,10), ethnic (11–13), and glucose tolerance categories (9,14–19).

In the evaluation of obesity, it has become apparent that it is not only the magnitude of the increase in fat mass, but also the site of distribution that is an important determinant of the development of insulin resistance and the conditions typically associated with obesity. Although a proportion of the variance in insulin sensitivity appears to be related to a central distribution of body fat, it has been debated whether this association is determined primarily by the accumulation of fat in the intra-abdominal or subcutaneous depots (16,20–24). We recently examined this issue in a large cohort of subjects who had central fat distribution, as determined by computed tomography (CT) scan and related to insulin sensitivity (10). In this cross-sectional analysis, we found that intra-abdominal fat (IAF) was a more important determinant of insulin sensitivity than was subcutaneous fat (SCF), whereas SCF was the more critical variable associated with leptin levels. In an important finding, we also observed that some individuals that were considered lean based on their BMI had increased amounts of IAF and were insulin resistant, suggesting that the relation between IAF fat and insulin sensitivity is a continuum that is not influenced by BMI.

The accumulation of central fat and presence of insulin resistance have both been associated with the dyslipidemia seen in the metabolic syndrome (25). Thus an increase in the waist-to-hip ratio (WHR) has been found to be associated with small dense LDL particles (26), as has been an increase in IAF mass (27,28) or insulin sensitivity (29,30). This pattern of central fat distribution has also been associated with an increase in VLDL and intermediate-density lipoprotein (IDL) (26,31) and a decrease in HDL_2 cholesterol (26,32,33). Although these analyses strongly suggest that central fat distribution and/or insulin resistance is an important determinant of adverse changes in lipoprotein profile, we believed that a critical examination of this issue in a large number of apparently healthy

TABLE 1
Subject characteristics

	LIS	LIR	OIR
n	65	73	58
M/F	21/44	28/45	26/32
Age (years)	49.1 ± 1.2	54.8 ± 1.4†	54.1 ± 1.2†
Weight (kg)	66.5 ± 1.4	70.8 ± 1.2*	89.3 ± 1.5‡,‖
BMI (kg/m^2)	23.3 ± 0.3	24.4 ± 0.2†	31.0 ± 0.4‡,‖
WHR	0.79 ± 0.01	0.82 ± 0.01*	0.89 ± 0.01‡,‖
SCF area (cm^2)	128.0 ± 7.9	189.5 ± 8.1‡	310.0 ± 17.2‡,‖
IAF area (cm^2)	51.0 ± 3.7	87.7 ± 4.9‡	166.1 ± 9.3‡,‖
Glucose (mmol/l)	5.2 ± 0.05	5.3 ± 0.04†	5.5 ± 0.05‡,§
Insulin (pmol/l)	39.4 ± 1.9	60.8 ± 3.6‡	82.8 ± 5.3‡,‖
S_I [$\times 10^{-5}$ min^{-1}/(pmol/l)]	11.18 ± 0.6	4.85 ± 0.17‡	3.62 ± 0.19‡,§

Data are means ± SE. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ vs. LIS; §$P < 0.05$, ‖$P < 0.001$ vs. LIR.

subjects was required to determine the impact of differences in body fat distribution and insulin sensitivity on plasma lipids. Further, we held that an assessment of these associations along with findings from small intervention studies would provide additional insight into the potential sequence of events in the development of an atherogenic lipoprotein profile. Therefore, we measured plasma lipoproteins, including an assessment of cholesterol distribution by density gradient ultracentrifugation (DGUC), in apparently healthy middle-aged men and women who were not receiving treatment for a lipid disorder and in whom we had also quantified insulin sensitivity and IAF. Here we describe the findings of this study and strongly suggest that IAF is a critical determinant of an atherogenic lipoprotein profile, including perturbations in the distribution of cholesterol in the different lipoprotein fractions.

RESEARCH DESIGN AND METHODS

Subjects. The study cohort was comprised of 196 individuals (75 men and 121 women) from the Greater Seattle area who had been recruited by advertisement to participate in a study of the effect of insulin sensitivity on lipoprotein profile alteration after egg consumption (34). Eligible subjects had to be apparently healthy with no history of diabetes or coronary or other vascular disease. In addition, they could not be receiving treatment for lipid disorders or hypertension and had to be free of renal or hepatic disease. At the time of screening, qualifying individuals had to have a fasting plasma glucose <6.4 mmol/l, LDL cholesterol <190 mg/dl, and triglycerides <500 mg/dl. Based on their BMI and insulin sensitivity index (S_I), subjects were divided a priori into three groups: lean insulin sensitive (LIS), lean insulin resistant (LIR), and obese insulin resistant (OIR), using cutoff points of 27.5 kg/m^2 and 7.0×10^{-5} min/(pmol/l), respectively. The cutoff point for obesity was determined using data from healthy populations and applying criteria set before the redefinition of overweight and obesity (NHANES II), and the cutoff point for insulin sensitivity was based on the highest value for this parameter among a group of apparently healthy obese subjects studied in Seattle (35).

Characterization of body size and fat distribution. A number of measures of body fat distribution were quantified. BMI was calculated as weight/height (kg/m^2). WHR was calculated as waist circumference (cm) divided by hip circumference (cm), using measurements made according to the techniques established by Krotkiewski et al. (36). The waist circumference was measured one-third up the distance between the umbilicus and the xiphoid process. The hip circumference was measured 4 cm below the superior anterior iliac crest.

SCF and IAF areas were quantified by a CT scan at the level of the umbilicus (14). The border of the intra-abdominal cavity was outlined on the CT image, and total fat and IAF areas were quantified by selecting an attenuation range of –250 to −50 Hounsfield units using standard software. The SCF area was calculated by subtracting the IAF area from total fat area. The variability of these measures made by a single observer is 1.5%, and day-to-day variability is < 1% (37).

Insulin sensitivity. S_I was determined using the minimal model of glucose kinetics described by Bergman and colleagues (38,39) from the glucose and insulin data obtained during a frequently sampled intravenous glucose tolerance test performed after an overnight fast. The test was modified by the injection of tolbutamide, which served to improve parameter identifiability (40). The day-to-day variability of S_I in our laboratory is 16.9% (41).

Chemical analyses. All analyses were performed on blood samples drawn after an overnight fast of at least 12 h. Samples were stored at −70°C until assayed.

Plasma glucose levels were measured using the glucose oxidase method. Plasma immunoreactive insulin levels were determined using a modification of the double antibody method of Morgan and Lazarow (42).

Plasma triglycerides and total cholesterol were measured by enzymatic analytical chemistry. HDL cholesterol was precipitated using dextran sulfate and measured enzymatically. LDL was calculated according to the Friedewald equation: LDL = TC – HDL – (TG/5), where TC is total cholesterol and TG is triglycerides. Apolipoprotein B was determined by nephelometry (43). Non-equilibrium DGUC was performed with the collection of 38 fractions in which cholesterol was measured (44). The LDL relative flotation (Rf), a measure of LDL particle buoyancy, was determined by dividing the fraction number containing the highest LDL cholesterol concentration by 38, the latter representing the total number of fractions sampled.

Statistical analyses. Comparison of demographic and metabolic variables among the LIS, LIR, and OIR groups and of lipoproteins across quartiles of body fat distribution and insulin sensitivity was performed by ANOVA, followed by Fisher's protected least significant differences test, where appropriate. The mean cholesterol differences at each of the 38 DGUC fractions were determined among groups using independent samples *t* test for equality of the means with a 95% confidence interval of the difference. Assessment of the relative contribution of IAF and SCF to S_I, and of S_I, IAF, SCF, and BMI to the cholesterol concentration in the individual DGUC fractions, was performed by multiple linear regression analysis. Data are presented as means ± SE unless stated otherwise. Data were considered significant at $P \leq 0.05$.

RESULTS

BMI, insulin sensitivity, and demographic measures. As shown in Table 1, the three groups had a similar number of subjects and similar gender distribution, but the LIS group was younger. The two lean groups were fairly well matched for BMI, but differed markedly for S_I, whereas the two insulin-resistant groups differed with regard to BMI and differed slightly with regard to S_I. Plasma glucose and insulin levels increased across groups with insulin resistance and obesity.

Body fat distribution and relationship with insulin sensitivity. The WHR and abdominal fat areas for the three groups are provided in Table 1. The WHR increased significantly from the LIS group to the LIR and OIR groups. Similarly, SCF and IAF areas increased significantly across the three groups. Thus, although the BMI measurements of the lean groups were similar, the CT scan demonstrated that the LIR group had more abdominal fat than the LIS group.

When all subjects were considered together, SCF and

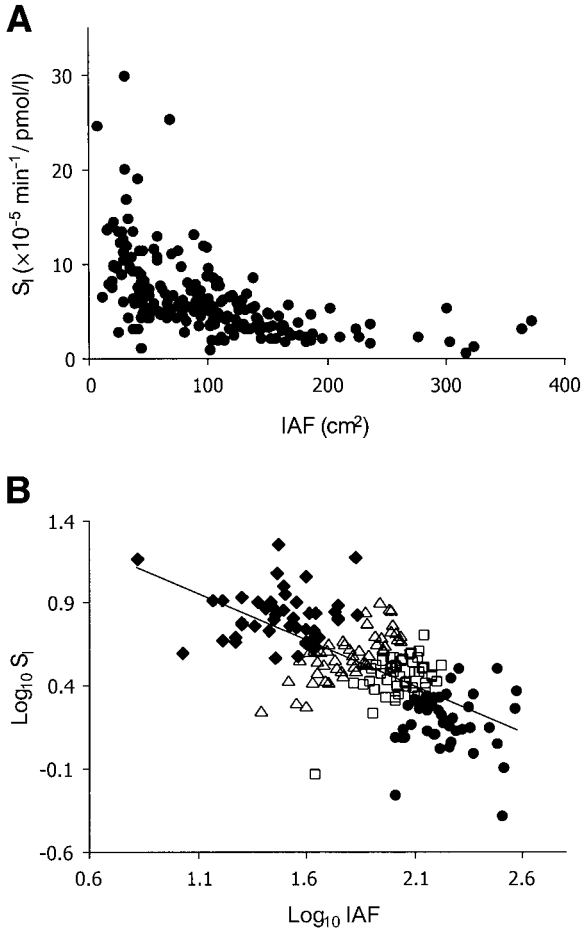

FIG. 1. Relationship between IAF and S_I in 196 individuals (75 men, 121 women). The two variables are related in a nonlinear manner (*A*) that is highly correlated ($r^2 = 0.438$, $P < 0.001$), as was demonstrated by log transformation (*B*). *B*: The interaction of S_I and IAF for each individual was determined as the quotient of the two variables; subjects were then subdivided into quartiles ($n = 49$ per group; ◆, △, □, ●) based on this interaction. The extreme quartiles represent a group that has the least IAF and is the most insulin sensitive (◆) and a group that has the most IAF and is the most insulin resistant (●).

IAF were linearly related ($r^2 = 0.192$, $P < 0.001$). The relationship between each of these two fat depots and S_I was curvilinear and best described by a logarithmic function. This relationship was greater for IAF versus S_I ($r^2 = 0.438$, $P < 0.001$) (Fig. 1) than for SCF versus S_I ($r^2 = 0.310$, $P < 0.001$). Using multiple linear regression analysis, IAF was found to contribute to this relationship, whereas SCF did not. Further, IAF and S_I were related in men ($r^2 = 0.528$, $P < 0.001$) and women ($r^2 = 0.383$, $P < 0.001$).

Lipoprotein measurements and relation to body fat distribution and insulin sensitivity. Plasma lipoprotein levels were consistent with a more atherogenic profile in the insulin-resistant subjects, and more so in the obese insulin-resistant individuals (Table 2).

To assess the relationship between body fat distribution and plasma lipoproteins and between S_I and plasma lipoproteins, we subdivided the cohort into quartiles based on IAF, SCF, BMI, and S_I measurements. As illustrated in Fig. 2, increasing IAF and decreasing S_I were both associated with the presence of a more atherogenic lipid profile. The change over quartiles for each lipoprotein variable was significant for both IAF and S_I ($P < 0.001$). Similarly, there were significant relationships between SCF and the plasma lipoproteins and BMI and the plasma lipoproteins that portended a more atherogenic lipid profile, with the exception that SCF was not related to HDL cholesterol, whereas BMI was not related to LDL cholesterol. The relationships between the different measures of body fat distribution and plasma lipoproteins was greatest for IAF for all measures except HDL cholesterol, where it was slightly greater with BMI than with IAF (ANOVA *F* test: 15.82 vs. 13.44).

Because the a priori classification of the subjects into LIS, LIR, and OIR groups based on BMI and S_I did not eliminate the confounding effect of abdominal obesity, and because IAF and S_I were highly correlated in a nonlinear manner (Fig. 1*A*), we calculated the quotient of S_I and IAF as a composite measure of each individual's value for these two parameters. For comparison purposes, we then divided the study population into four equal-sized groups ($n = 49$) based on the interaction of their individual measures of IAF and S_I (Fig. 1*B*). The individuals in the two extreme quartiles differed markedly for this composite measure of IAF and S_I, which allowed us to compare a group of subjects with the least IAF (34.3 ± 2.0 cm^2) who were the most insulin sensitive [11.73 ± 0.71 × 10^{-5} min^{-1}/(pmol/l)] with a group of subjects with the most IAF (182.5 ± 9.7 cm^2; $P < 0.001$) who were the most insulin resistant [2.86 ± 0.14 × 10^{-5} min^{-1}/(pmol/l); $P < 0.001$]. The group that was the most insulin resistant and had the most IAF had a more atherogenic lipoprotein profile than the group that was the most insulin sensitive and had the least IAF. Thus, in the group with the most IAF that was the most insulin resistant, the triglyceride (177.8 ± 13.5 vs. 75.8 ± 4.8 mg/dl; $P < 0.001$), total cholesterol (210.5 ± 5.3 vs. 182.6 ± 5.1 mg/dl; $P < 0.001$), LDL cholesterol (130.1 ± 4.7 vs. 106.0 ± 4.1 mg/dl; $P < 0.001$), and apolipoprotein B (107.9 ± 3.5 vs. 79.8 ± 2.6 mg/dl; $P < 0.001$) levels were increased, whereas the HDL cholesterol level was de-

TABLE 2
Lipoprotein measurements

	LIS	LIR	OIR
n	65	73	58
Triglycerides (mg/dl)	88.5 ± 7.4	117.3 ± 7.4*	161.4 ± 12.0‡,‖
Total cholesterol (mg/dl)	187.9 ± 4.5	209.3 ± 3.7‡	206.4 ± 4.8†
LDL cholesterol (mg/dl)	111.1 ± 3.6	132.1 ± 3.0‡	128.9 ± 4.2‡
HDL cholesterol (mg/dl)	58.7 ± 1.9	53.3 ± 1.6*	44.8 ± 1.4‡,‖
Apolipoprotein B (mg/dl)	85.0 ± 2.6	100.7 ± 2.3‡	105.2 ± 3.3‡
Rf	0.288 ± 0.003	0.278 ± 0.004*	0.262 ± 0.004‡,§

Data are means ± SE. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ vs. LIS; §$P < 0.01$, ‖$P < 0.001$ vs. LIR.

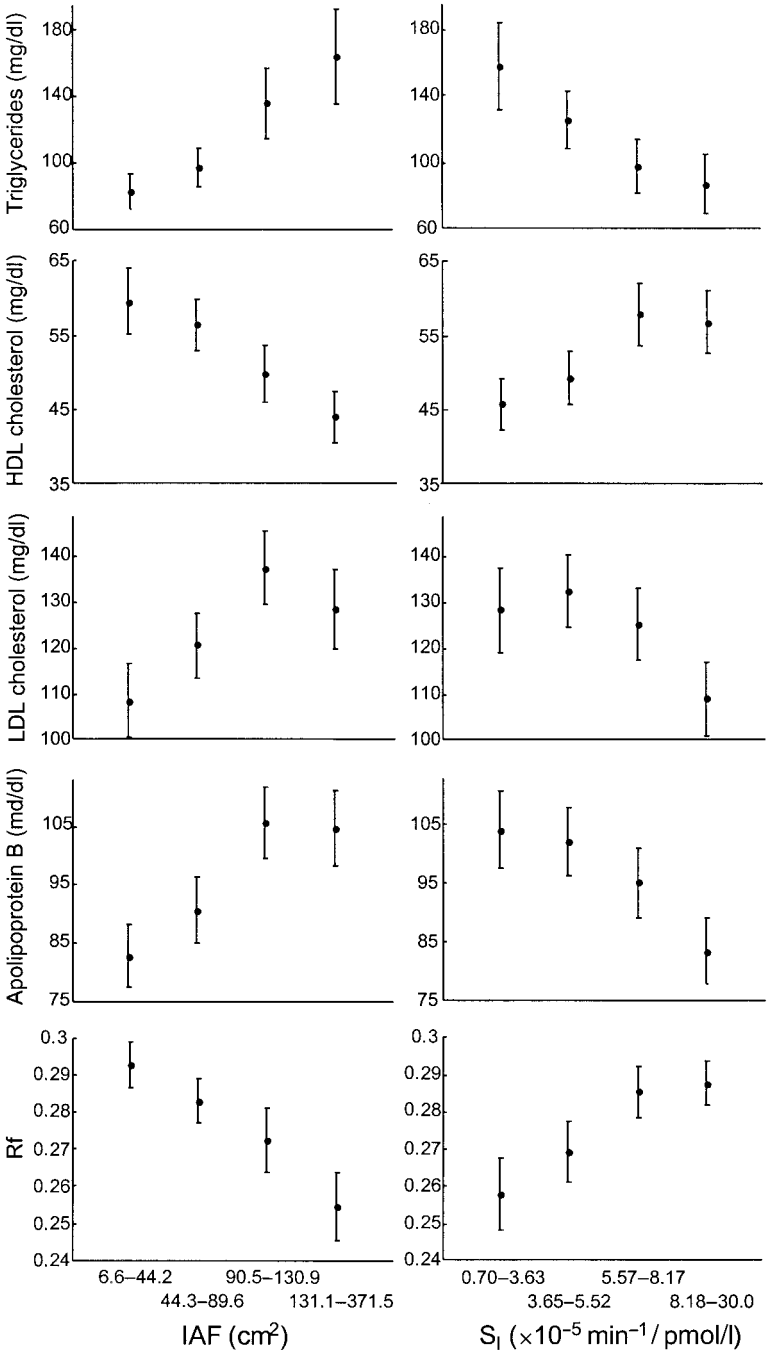

FIG. 2. Relationship between IAF area (*left panels*) and S_I (*right panels*) and different lipoproteins in 196 individuals. The whole cohort was subdivided into quartiles for IAF area and S_I. The range for each quartile is listed. Data are means ± SE, with 95% confidence interval bars. Increasing IAF area and decreasing S_I are associated with a more atherogenic profile for each lipoprotein. For each lipoprotein variable, the change across quartiles was significant ($P < 0.001$).

creased (44.4 ± 1.8 vs. 60.9 ± 2.2 mg/dl; $P < 0.001$) as was the measure of LDL buoyancy distribution (Rf: 0.252 ± 0.005 vs. 0.294 ± 0.003; $P < 0.001$), when compared to the group that had the least IAF and was the most insulin sensitive. These two subject groups also differed markedly for BMI (most IAF, most insulin resistant: 29.6 ± 0.6 kg/m^2 vs. least IAF, most insulin sensitive: 22.9 ± 0.3 kg/m^2; $P <$ 0.001). However, BMI made no additional contribution beyond that of IAF and S_I in determining the above differences in the lipoproteins between the group that was the most insulin resistant and had the most IAF and the group that was the most insulin sensitive and had the least IAF.

DGUC analysis. The DGUC analysis allowed us to compare the lipoprotein cholesterol levels encompassing 38 fractions in the two groups that were defined based on the interaction of IAF and S_I. When the cholesterol distribution in the most intra-abdominally obese, insulin-resistant group was compared with that in the most intra-abdominally lean, insulin-sensitive group, significant differences were observed in almost all fractions across the density gradient (Fig. 3). The most intra-abdominally obese, insulin-resistant group had more cholesterol in the VLDL, IDL, and dense LDL fractions. In addition, they had less cholesterol in the HDL fractions. Significant differences in the cholesterol content were maintained in fractions 1–4, 7–9, 23, 25, 26, and 29–38 after adjustment for the effect of BMI.

To determine the relative contributions of IAF and S_I to the cholesterol levels in the DGUC fractions, we performed multiple linear regression analyses for each fraction using data from the whole cohort. In the first model,

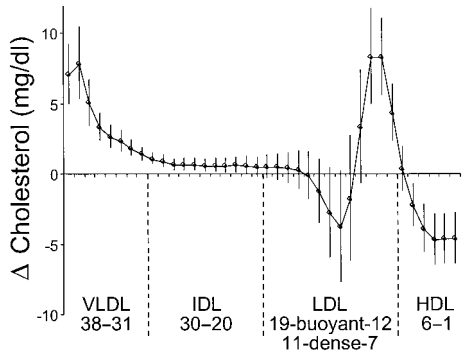

FIG. 3. Difference plots of the cholesterol concentration in 38 DGUC fractions for intra-abdominally obese, insulin-resistant subjects and intra-abdominally lean, insulin-sensitive subjects (n = 49 per group). The two groups represent the extreme quartiles for the quotient of S_I and IAF, a composite measure that was determined for each individual (see Fig. 1*B*). Data are means ± SE, with 95% confidence interval bars. The different fractions and their representation of the different cholesterol-containing lipoproteins are illustrated. The intra-abdominally obese, insulin-resistant group had more cholesterol in the VLDL, IDL, and dense LDL fractions and less cholesterol in the HDL fractions.

in which IAF and S_I were the only independent variables and the fractional cholesterol concentration was the dependent variable, the cholesterol concentration in the fractions corresponding to the VLDL, IDL, dense LDL, and HDL fractions was associated with IAF after adjustment for S_I (Fig. 4*A*). In this model, after adjustment for IAF, S_I contributed independently to some of the fractions corresponding to VLDL (fractions 32 and 34–36), but not to those in the IDL, LDL, or HDL ranges (Fig. 4*B*). In the second model, we included SCF as an independent variable along with IAF and S_I, with the fractional cholesterol concentration again being the dependent variable. In this model, the cholesterol concentration in the fractions corresponding to VLDL (fractions 31–38), IDL (fractions 29 and 30), buoyant LDL (fractions 12–14), dense LDL (fractions 7–9), and HDL (fractions 1–5) was associated with IAF, whereas S_I made no additional contribution to any of the fractions. In a third model, we included BMI as an independent variable together with IAF, S_I, and SCF, and found that the cholesterol concentration in the fractions corresponding to VLDL (fractions 31–38), IDL (fraction 30), and dense LDL (fractions 8–10) was associated with IAF, whereas S_I again made no additional contribution. Thus IAF, but not S_I, had independent effects to determine the cholesterol concentration beyond those of SCF and BMI.

DISCUSSION

By studying 196 apparently healthy subjects who differed in body habitus and insulin sensitivity, we were able to examine the relationship of these variables to the lipoprotein profile. We found that both obesity and insulin sensitivity are determinants of the lipoprotein profile, with an increased amount of IAF and insulin resistance being associated with a more atherogenic lipid profile: increased triglyceride, total cholesterol, LDL cholesterol, and apolipoprotein B levels and a decreased HDL cholesterol level and Rf (a measure of LDL buoyancy distribution). We were also able to extend the analysis by performing DGUC and examining the effect of differences in IAF and insulin sensitivity on the amount of cholesterol in the different lipoprotein fractions. This analysis revealed that subjects who had greater amounts of IAF and a lower S_I had more cholesterol in the VLDL, IDL, and dense LDL fractions but less cholesterol in the HDL fractions. Further, the cholesterol in the VLDL, IDL, dense LDL, and HDL fractions was more strongly associated with IAF than with insulin sensitivity, the relation of the latter two being highly colinear. Insulin sensitivity did contribute to the cholesterol concentration in the VLDL range. When the effect of SCF was also accounted for, we found that IAF was still a determinant of VLDL, IDL, buoyant LDL, dense LDL, and HDL, whereas insulin sensitivity made no contribution to the cholesterol concentration. Finally, when SCF and the role of body size, quantified as BMI, were considered, IAF was still an independent determinant of VLDL, IDL, and dense LDL, whereas insulin sensitivity did not contribute to the cholesterol concentration. Thus it appears that IAF and insulin sensitivity are associated with an atherogenic lipid profile, with the effect of obesity being largely attributable to IAF.

The subjects we studied were recruited from the general population and were classified a priori into three groups based on their BMI and S_I values. This classification and the subsequent analyses allowed us to make a number of observations about the relationship between obesity and insulin resistance and, in turn, the association of body habitus and insulin sensitivity to plasma lipoproteins. First, it is apparent that BMI cannot be used as a simple means of determining whether an individual is or is not likely to have a lipoprotein profile associated with an

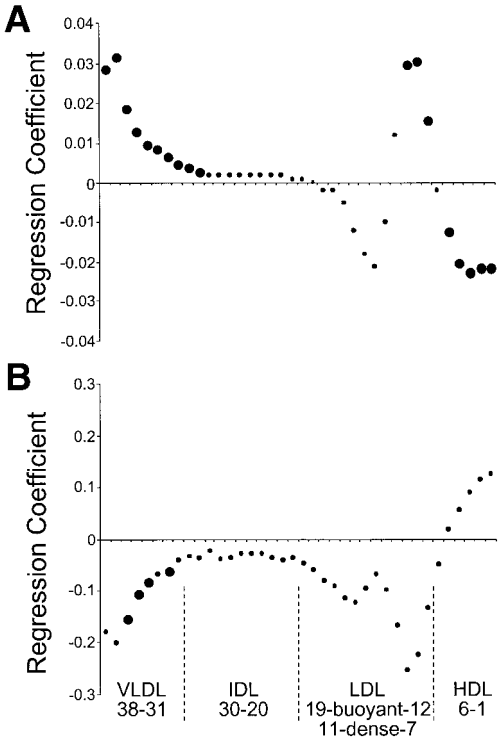

FIG. 4. Multiple linear regression analysis of the cholesterol content of each DGUC fraction, with IAF area and S_I as the independent variables. The regression coefficients for each of the 38 fractions are plotted for IAF (*A*) and S_I (*B*). The different fractions and their representation of the different cholesterol-containing lipoproteins are illustrated. Larger points represent statistically significant relationships determined by multiple linear regression analysis in which the one independent variable has been adjusted for the other ($P < 0.05$).

increased risk of atherosclerosis. Apparently "lean" individuals can be insulin resistant and have increased amounts of IAF, with this characterization being associated with an adverse lipoprotein profile. Second, in insulin-resistant subjects, an increase in body size (based on BMI) is associated with a further change in the lipoprotein profile, specifically an increase in triglycerides and a decrease in both HDL cholesterol and Rf, but no increase in LDL cholesterol, which is consistent with an additional increase in atherogenic risk. This finding is in keeping with the well-recognized role of obesity as an important risk factor for cardiovascular disease (45). Third, IAF and S_I are highly correlated in a curvilinear manner, and this relationship is continuous irrespective of body size or sex. In turn, the phenotype of intra-abdominal obesity and insulin resistance is associated with a more atherogenic lipid profile. Fourth, SCF is increased in lean subjects who are insulin resistant compared with those who are insulin sensitive, and is further increased in individuals who are obese and insulin resistant. In addition, because SCF and IAF are positively and linearly related, they both increase as S_I declines. However, IAF is more strongly related to S_I, and therefore it would appear that IAF is more strongly associated with an adverse lipoprotein profile than is SCF, the latter more likely reflecting total body fat (46).

There has been a great deal of interest in the role of insulin resistance in the pathogenesis of a number of disorders, including type 2 diabetes, hypertension, and dyslipidemia, based on the clear association between insulin resistance and these conditions. A number of different names have been suggested to describe the constellation of associations between insulin resistance and these clinical findings, including syndrome X (6), the insulin resistance syndrome (47), the central adiposity syndrome (48), and the metabolic syndrome (25). In the course of these investigations, the roles of insulin resistance and central body fat distribution have been discussed, but a clear delineation of their roles in determining an atherogenic lipoprotein profile has not been achieved. The present study has provided a rather unique opportunity to further address these associations as it combines sophisticated, discriminatory measures of insulin sensitivity, body fat distribution, and plasma lipoproteins with a large cohort of subjects. Our findings regarding the relationship between IAF and insulin resistance with lipoprotein abnormalities is supported by intervention studies. Caloric restriction, which results in weight loss and decreased IAF, results in an improvement in an atherogenic lipid profile (49–54). However, the changes that follow caloric restriction are compounded somewhat by the fact that insulin sensitivity also improves with weight loss (53,55,56). Similarly, exercise training, which improves the lipoprotein profile, is also associated with reductions in body weight and IAF as well as an increase in insulin sensitivity (37,52,57,58). Both increased IAF and insulin resistance have been associated with increased hepatic lipase activity (33,59,60), leading to small dense LDL and decreased HDL_2 cholesterol levels (61–64); maneuvers to decrease hepatic lipase correct this dyslipidemia (53,65).

Collectively, previous intervention studies and the present cross-sectional analysis in a large cohort in whom discriminatory measures were used for quantification do provide insight into these relationships. They strongly suggest that an abnormality in body fat distribution leads to the accumulation of intra-abdominal adiposity, which in turn is associated with the development of insulin resistance, followed by dyslipidemia. IAF would therefore be a contributor to an adverse lipoprotein profile and, thus, cardiovascular risk. To confirm whether insulin sensitivity is an intermediate step in IAF's effect or whether IAF has independent effects will require further study.

In summary, using a cross-sectional approach in a large cohort of apparently healthy subjects, we found that IAF appears to be a major determinant of an atherogenic lipid profile. Although insulin resistance is also associated with an adverse lipid profile, it would appear that this association is largely based on the fact that this parameter and IAF are closely correlated. However, it is possible that insulin sensitivity may play an additional contributory role in determining changes in cholesterol content in the VLDL fraction. Finally, these results suggest that approaches aimed at reducing IAF, via lifestyle or medication, would have a beneficial effect on both insulin sensitivity and plasma lipoproteins. Whether a similar relationship between IAF and insulin sensitivity holds for other features of the metabolic syndrome will await further evaluation.

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