Relationships Between Insulin Resistance and Lipoproteins in Nondiabetic African Americans, Hispanics, and Non-Hispanic Whites: The Insulin Resistance Atherosclerosis Study

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The study purpose was to explore the association between dyslipidemia and insulin resistance in three ethnic groups. The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter epidemiologic study conducted at four clinical centers in California, Texas, and Colorado. The study population for this analysis consisted of 931 non-Hispanic white, African American, and Hispanic men and women (aged 45 to 64 years) without diabetes. The IRAS clinical examinations included lipoprotein measures, a 75-g glucose tolerance test, and the frequently sampled intravenous glucose tolerance (FSIGT) test. The results show a consistent relationship between insulin-mediated glucose disposal and dyslipidemia in African American, Hispanic, and non-Hispanic white men and women. Further, LDL size was inversely associated with insulin resistance in all three ethnic groups. These findings indicate that dyslipidemia is a fundamental part of the insulin resistance syndrome in all of the ethnic groups studied.

THE INSULIN RESISTANCE SYNDROME is recognized as an underlying cause of non–insulin-dependent diabetes mellitus and atherosclerosis. This syndrome is associated with a constellation of metabolic abnormalities, the most prominent of which is dyslipidemia. Dyslipidemia may increase susceptibility to atherosclerosis in insulin-resistant individuals. There is a relationship between insulin resistance and an elevated concentration of very–low-density lipoprotein (VLDL) and a low concentration of high-density lipoprotein (HDL) cholesterol. This relationship was first proposed by Reaven et al.[1,2] The relationship between lipoproteins and insulin action was reported in a cohort of American Indians[3] and then confirmed in three additional studies in white subjects.[4-6] A more recently described third component of the dyslipidemia, the presence of small, dense low-density lipoprotein (LDL), has been shown to have a direct relationship with insulin resistance in studies of white men and women.[7,8]

To understand the extent of dyslipidemia in individuals with insulin resistance and to properly guide the therapeutic approaches, it is important to know whether the dyslipidemia is associated with insulin resistance in other ethnic groups. The Insulin Resistance Atherosclerosis Study (IRAS) was initiated to assess the relationship between insulin resistance and risk factors for atherosclerosis in three groups: African Americans, Hispanics, and non-Hispanic whites. This report presents results for the relationship between direct measures of insulin action and lipoproteins in nondiabetic subjects in these three ethnic groups.

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SUBJECTS AND METHODS

The design and methods of the IRAS have been published previously.[9] Briefly, this epidemiologic study was conducted at four clinical centers. African Americans and non-Hispanic whites were studied in Oakland and Los Angeles, California, and Hispanics and non-Hispanic whites were studied in San Luis Valley, Colorado, and San Antonio, Texas. The latter were recruited from the San Luis Valley Diabetes Study[10] and the San Antonio Heart Study.[11] The IRAS population contained 1,625 individuals, but in this analysis (see the Statistical Analysis), the sample population numbered 931. The following were excluded: individuals with diabetes (n = 537), those who had no recorded value for insulin sensitivity (S_I) (n = 85), and those who were taking lipid-lowering drugs (n = 72). The study was approved by the institutional review boards of all four clinical centers, and informed consent was obtained for all subjects.

Clinical Examination

The IRAS clinical examination consisted of two 4-hour visits scheduled approximately 1 week apart.[12] Before each visit, participants were asked to refrain from alcohol and heavy exercise for 24 hours, from food for 12 hours, and from smoking on the morning of the examination. The first visit included a 75-g oral glucose tolerance test; blood was collected for fasting and 2-hour glucose samples. To measure insulin resistance, participants underwent the frequently sampled intravenous glucose tolerance test (FSIGT)[13] on the second visit. Glucose tolerance status was classified according to World Health Organization criteria.[14] Race and ethnicity were self-reported. Anthropometric measurements (height, weight, and waist and hip circumferences) were obtained using a standard protocol. The body mass index ([BMI] kilograms per meter squared) was used to measure adiposity, and the waist to hip ratio (WHR) was used to measure body fat distribution.

Glucose and insulin levels were measured at the central IRAS laboratory at the University of Southern California. Two modifications of the original FSIGT protocol[15,16] were used. The first involved the use of insulin instead of tolbutamide injection to ensure adequate plasma insulin levels for accurate computation of insulin resistance across a broad range of glucose tolerance.[17] As determined in a previous study,[18]

this modified protocol is a valid and reliable index of S_I compared with the euglycemic clamp, although its reliability is slightly lower in patients with diabetes.[18,19] The second modification involved the use of a reduced sampling protocol (12 instead of 30 plasma samples, which had results similar to those of the full protocol[20]) because of the large number of subjects. A 50% glucose solution (0.3 g/kg) and regular human insulin (0.03 U/kg) were administered intravenously at 0 and 20 minutes, respectively. Blood was collected at -5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes for plasma glucose and insulin measurements.

Laboratory Analysis

The plasma glucose level was measured using the glucose oxidase technique on an automated autoanalyzer (Yellow Springs Instruments, Yellow Springs, OH), and the insulin level was determined with the dextran-charcoal method of Herbert et al.[21] The insulin assay used in this study has a high degree of cross-reactivity with proinsulin.[12]

Insulin sensitivity, expressed as S_I and glucose sensitivity (S_G) was calculated using minimal model analysis (MINMOD, version 3.0, 1994), a program that uses a nonlinear least-squares estimation technique to yield parameter estimates and the precision of their estimation. FSIGTs were performed with a 0.03-U/kg insulin injection. The intratest patterns of insulin and glucose levels were assayed in the IRAS central laboratory, and these values were used to estimate the parameters of the minimal model. The model consists of two differential equations and has four parameters that are estimated from the FSIGT. The ratio of two of these parameters, p_3/p_2, is accepted as an accurate measure of S_I.[18] The index, S_G, is a measure of the ability of glucose to enhance its own disappearance at basal insulin.[22]

Plasma lipoprotein measurements were obtained from single fresh plasma samples using Lipid Research Clinic methods. All laboratory measurements were analyzed at the Penn Medical Laboratories of Medlantic Research Institute (Washington, DC). LDL and HDL were isolated by isopycnic ultracentrifugation, and VLDL (top) and bottom fractions were used for measurement of cholesterol and triglyceride concentrations.[23] The HDL cholesterol level was measured in the presence of manganese chloride and heparin in which non-HDL lipoproteins were precipitated, leaving HDL in the supernatant. The supernatant was removed after centrifugation, and the cholesterol level was measured on a separate autoanalyzer channel set to measure low cholesterol values. LDL was calculated as the difference between the HDL cholesterol and the bottom cholesterol. Triglyceride levels were measured enzymatically after correction for free glycerol.[23]

LDL size distribution (ie, distribution of the diameter of the major LDL peak for each participant) was determined using the method of Krauss and Burke.[24] Plasma samples were stored at −70°C until LDL size analyses were completed. Gradient gels obtained from Isolab (Akron, OH) were used for routine quantification. The measurement of the size of the predominant peak was calibrated using LDL subfractions. Analytical centrifugation, performed at the Donner Laboratories (Berkeley, CA), was used to determine the molecular diameter of LDL subfractions and to standardize the controls. The LDL size of the predominant peak for an individual was defined as that subject's LDL size. Three models were used to assess the relationships, adjusting for age and then for obesity and body fat distribution.

Statistical Analysis

Because of the possible confounding effect of the action of hyperglycemia and other metabolic complications of hyperglycemia on lipoprotein concentrations, individuals with diabetes were eliminated from the analysis of the relationship of insulin sensitivity and lipoprotein concentration and composition. Initial analyses were stratified by gender. For each outcome (lipoprotein) variable, tests for $S_I \times$ ethnicity $\times$ clinic interaction were performed. No three-way interaction effects were significant (all $P > .1$). Therefore, two-way tests for interaction (clinic $\times S_I$) were evaluated in models adjusted for age and BMI. No clinic $\times S_I$ interaction tests were significant (all $P > .1$). Coefficients relating lipoproteins to S_I were calculated for each ethnic/clinic combination using cell means linear models.[25] Because there were no significant clinic $\times S_I$ interaction effects, we collapsed the analyses into two clinic groups. Coefficients relating lipoproteins to S_I were compared between non-Hispanic whites and African Americans (Oakland + Los Angeles) and between non-Hispanic whites and Hispanics (San Luis Valley and San Antonio) by taking appropriate combinations of cell means coefficients. Successive regression models were fit, adjusting for age, age + BMI, and age + BMI + WHR. The predicted direction of these associations and their statistical significance are listed in Table 2, and the relative magnitude of these associations is shown in Table 3. The PROC GLM component of the SAS statistical software[26] was used for all regression models.

To describe the differences in lipoprotein values that result from different values for S_I, predicted values for lipoprotein measures were calculated by substituting the 25th and 75th percentiles of S_I into the fitted regression equations. Because regression models were adjusted for age and anthropometric measures, the mean values for age, BMI, and WHR were substituted into the appropriate models. Predicted differences in mean lipoprotein values were then calculated by subtracting the predicted lipoprotein value at the 25th percentile of S_I from the predicted value at the 75th percentile of S_I. Similar analyses and predicted values were calculated for the logarithm of fasting insulin in place of S_I to compare the relative strength of S_I and fasting insulin in predicting lipoprotein measures. Natural logarithmic transformations of VLDL triglyceride, triglyceride, and HDL cholesterol were necessary to satisfy statistical assumptions. Statistical significance was defined as P less than .05.

RESULTS

Data for demographic variables, lipoprotein concentrations, and measures of insulin action are shown by gender and ethnic group in Table 1. By design, all groups are of similar age. Within genders, ethnic groups are similar with respect to obesity and fasting glucose. Because of the IRAS sampling scheme, individuals with impaired glucose tolerance were oversampled relative to those with normal glucose tolerance. The sample group is therefore relatively insulin-resistant, as indicated by high fasting insulin concentrations and by a high WHR, especially among women. Data for insulin action as measured by S_I confirm that the group is insulin-resistant, and more so in African American and Hispanic men and women than in non-Hispanic whites.[11]

We first assessed the relationships between plasma lipoproteins and insulin resistance separately in each gender and ethnic group by computing slopes for the relationship between each lipoprotein and insulin-mediated glucose disposal as measured by S_I, adjusted for age alone, age + BMI, and age + BMI + WHR (Table 2). In all gender/ethnic groups, there was a negative relationship between total triglycerides and S_I. Conversely, in all groups, there was a positive relationship between HDL cholesterol and S_I. Although they did not all reach statistical significance, the magnitude of these relationships did not differ significantly in any of the gender/ethnic groups. There appeared to be more variability in the β coefficients relating LDL size and S_I. These were consistently positive except in non-Hispanic whites in Oakland and Los Angeles. Relationships between the three lipoprotein variables and S_G and acute insulin response were assessed, but no significant relationships

Table 1. Demographic and Physiologic Variables by Gender and Region/Ethnicity: The IRAS

Variable	Oakland /Los Angeles		San Luis Valley/ San Antonio	
	African American	Non-Hispanic White	Hispanic	Non-Hispanic White
Male (n)	96	94	142	78
Age (yr)	54 ± 9	55 ± 8	54 ± 9	55 ± 8
BMI (kg/m^2)	29 ± 5	27 ± 4	28 ± 5	27 ± 4
WHR	0.90 ± 0.05	0.91 ± 0.06	0.95 ± 0.05	0.93 ± 0.06
Fasting glucose (mg/dL)	104 ± 13	103 ± 9	99 ± 10	98 ± 10
Fasting insulin (μU/mL)*	17 ± 11	13 ± 6	19 ± 23	13 ± 8
S_I (MINMOD)	1.9 ± 1.8	2.4 ± 1.9	1.9 ± 2.1	2.2 ± 1.6
VLDL cholesterol (mg/dL)*	21 ± 16	24 ± 17	31 ± 24	30 ± 25
VLDL cholesterol/triglyceride ratio*	0.28 ± 0.09	0.25 ± 0.09	0.23 ± 0.06	0.24 ± 0.06
VLDL triglycerides (mg/dL)	77 ± 47	102 ± 65	147 ± 121	126 ± 102
Triglycerides (mg/dL)*	109 ± 58	126 ± 63	173 ± 114	148 ± 96
LDL cholesterol (mg/dL)	147 ± 39	142 ± 31	137 ± 34	141 ± 38
LDL size (Å)	261 ± 9	258 ± 11	257 ± 10	260 ± 10
HDL cholesterol (mg/dL)*	45 ± 16	43 ± 14	38 ± 12	40 ± 13
Female (n)	140	95	186	100
Age (yr)	53 ± 8	55 ± 8	54 ± 8	57 ± 9
BMI (kg/m^2)	30 ± 7	28 ± 7	29 ± 6	28 ± 5
WHR	0.80 ± 0.07	0.80 ± 0.07	0.82 ± 0.06	0.80 ± 0.06
Fasting glucose (mg/dL)	100 ± 12	98 ± 13	95 ± 10	94 ± 11
Fasting insulin (μU/mL)*	18 ± 19	13 ± 10	17 ± 12	16 ± 18
S_I (MINMOD)	2.0 ± 1.8	3.2 ± 3.0	2.0 ± 1.8	2.1 ± 1.5
VLDL cholesterol (mg/dL)*	14 ± 12	19 ± 17	24 ± 17	22 ± 14
VLDL cholesterol/triglyceride ratio*	0.28 ± 0.16	0.24 ± 0.09	0.25 ± 0.09	0.27 ± 0.11
VLDL triglycerides (mg/dL)	58 ± 47	84 ± 75	103 ± 74	87 ± 55
Triglycerides (mg/dL)*	88 ± 48	112 ± 65	136 ± 66	128 ± 68
LDL cholesterol (mg/dL)	146 ± 32	139 ± 34	136 ± 37	139 ± 32
LDL size (Å)	265 ± 9	262 ± 11	261 ± 9	262 ± 9
HDL cholesterol (mg/dL)*	55 ± 15	56 ± 18	47 ± 13	49 ± 12

NOTE. Data are presented as the mean ± SD.

*Data subsequently analyzed as $\log_e$-transformed values.

were observed (data not shown). Relationships between fasting insulin and lipoproteins were similar to those observed for S_I (data not shown). The relationships of VLDL triglycerides and VLDL cholesterol to S_I were similar to those for total triglycerides and are therefore not shown. There was no association between LDL concentration and S_I. There were no significant $S_I \times$ gender interactions for any of the lipoprotein variables in any of the models ($P > .2$).

Because no gender or ethnic differences were observed in the relationships between lipids and S_I, analyses were repeated for the combined group. Three models were examined. The first included adjustments for age, gender, and ethnicity. Sequential additional adjustments for BMI and WHR were included in the second and third models. Table 3 presents the data for predicted changes in triglycerides, HDL, and LDL size, comparing individuals at the 25th and 75th percentiles of S_I. Compared with subjects at the 25th percentile, those at the 75th percentile had 18 mg/dL lower triglycerides, 3.5 mg/dL higher HDL, and 1 Å larger LDL. These differences were only slightly modulated by adjusting for BMI and WHR. We also assessed these relationships by comparing individuals at the 25th and 75th percentiles of fasting insulin and found results of similar strength. The opposing direction of the lipoprotein associations for S_I and fasting insulin is expected given the inverse association between S_I and fasting insulin. These associations did not differ by ethnicity or by gender.

DISCUSSION

This is the first study to present results on the relationships between measures of insulin action and lipoproteins in the three major ethnic groups in the United States. The results show a consistent relationship between insulin-mediated glucose disposal and dyslipidemia in men and women in all three groups. Those with insulin resistance have higher total and VLDL triglycerides, lower HDL cholesterol, and smaller LDL size. The relationships of VLDL triglycerides and VLDL cholesterol to S_I were similar to those for total triglycerides. Population-based studies that examined relationships among fasting insulin concentrations, triglycerides, and HDL cholesterol suggest that dyslipidemia is consistently observed in all ethnic groups.[27-37]

This report presents clear evidence of these relations using a direct measure of insulin action, and extends the findings to include the presence of small, dense LDL. Small LDL particles thus appear to be a fundamental component of the dyslipidemia of insulin resistance in both sexes and in all ethnic groups studied.

A body of in vitro and metabolic data provides information on mechanisms for the dyslipidemia that accompanies insulin resistance. Initial consideration of the association between triglycerides and insulin action included the suggestion that the relationship may be explained by direct stimulation of VLDL production by insulin.[38,39] Chronic ambient hyperinsulinemia

Table 2. Slope Estimates for Log_e Values Versus S_I for Males and Females: The IRAS

	β Coefficient			
	Oakland/Los Angeles		San Luis Velley/San Antonio	
Parameter	African American (n = 96)	Non-Hispanic White (n = 94)	Hispanic (n = 142)	Non-Hispanic White (n = 78)
Triglycerides				
Male, adjusted for				
Age	−0.052	−0.040	−0.085†	−0.146†
Age + BMI	−0.034	−0.029	−0.065*	−0.129†
Age + BMI + WHR	−0.025	−0.012	−0.047	−0.108†
Female, adjusted for				
Age	−0.100†	−0.066†	−0.094†	−0.120†
Age + BMI	−0.092†	−0.056*	−0.086†	−0.110†
Age + BMI + WHR	−0.066†	−0.041	−0.067†	−0.078†
HDL cholesterol				
Male, adjusted for				
Age	0.025	0.052†	0.035*	0.028
Age + BMI	0.013	0.045†	0.021	0.016
Age + BMI + WHR	0.008	0.036*	0.012	0.006
Female, adjusted for				
Age	0.047†	0.037†	0.060†	0.058†
Age + BMI	0.037†	0.035†	0.047†	0.044†
Age + BMI + WHR	0.024	0.028*	0.038†	0.029
LDL size				
Male, adjusted for				
Age	0.665	−0.038	0.281	1.103
Age + BMI	0.589	−0.086	0.202	1.031
Age + BMI + WHR	0.570	−0.120	0.163	0.989
Female, adjusted for				
Age	0.202	0.941*	1.072†	1.100
Age + BMI	0.170	1.083*	1.050†	1.058
Age + BMI + WHR	−0.032	0.970*	0.900*	0.825

NOTE. *P* values are for the test of whether the slope equals 0. For assessment of the magnitude of these effects, refer to Table 3.

*$P < .05$.

†$P < .01$.

secondary to insulin resistance might directly contribute to hypertriglyceridemia. However, studies in isolated hepatocytes consistently demonstrate an inhibitory effect of insulin on VLDL production.[40] Intensive insulin therapy in people with diabetes almost always results in a decrease of triglycerides.[41] Lewis et al[42] demonstrate that infusion of insulin in vivo directly results in a lower rate of VLDL triglyceride and apolipoprotein (apo) B production.

Several lines of evidence suggest that the insulin-resistant state itself induces elevated VLDL. Insulin resistance is strongly associated with central obesity.[43,44] Centrally obese individuals often have increased fatty acid flux through the splanchnic area,[45] and an elevation in free fatty acids increases VLDL triglyceride levels and apo B production in humans.[38] Additional support for this scenario is derived from IRAS data on postload free fatty acid concentrations, which are strongly correlated with insulin action and triglyceride concentrations in the manner one would expect if free fatty acid concentrations mediate, at least in part, the association between insulin resistance and triglyceride concentrations.[46] Finally, in individuals with insulin resistance, the activity of lipoprotein lipase, an insulin-dependent enzyme, may be decreased,[47] thus impeding VLDL clearance.

Inadequate understanding of the key mechanisms regulating HDL metabolism impedes elucidation of the associations between insulin resistance and HDL. VLDL and HDL are inversely related in most individuals, and it is well established that factors which interfere with VLDL metabolism or elevate VLDL result in decreased HDL. However, several reports demonstrate that the relationships between HDL and insulin are independent of VLDL concentrations.[3,5] Thus, there may be a direct connection between insulin resistance and HDL metabolism. This is unlikely to be mediated through insulin concentrations, because exogenous insulin therapy usually leads to abnormally high HDL.[48] Possible mechanisms for the lower HDL in insulin resistance center around hepatic triglyceride lipase activity, which is intimately related to HDL clearance and is elevated in individuals with insulin resistance.[49] Lower cholesterol ester transfer protein (CETP) and/or lecithin cholesterol acyltransferase (LCAT) activity in insulin-resistant individuals could also result in lower HDL concentrations. In a study of the effects of acute endogenous hyperinsulinemia on plasma CETP and phospholipid transfer protein (PLTP) in eight male subjects, Van Tol et al[50] found that hyperglycemia-induced hyperinsulinemia does not affect CETP activity levels. On the other hand, Dullaart et al[51] noted an increase in CETP and PLTP activity in obese men compared with non-obese men, with no significant change in LCAT activity. The latter showed a positive correlation between CETP and the fasting C-peptide concentration, another surrogate for insulin resistance.

Although the relationship between LDL size and S_I was more variable, LDL size increased with S_I in all ethnic groups. There are several possibilities to explain this finding. The small LDL might result from some of the alterations in VLDL metabolism already discussed, because almost all studies have demonstrated a consistent inverse association between VLDL concentration and LDL size. The metabolic mechanisms controlling the size of LDL are not well understood. One possibility is that if there is impaired lipase activity in insulin-resistant subjects, the persistence of VLDL remnants may result in smaller LDL particles.

Table 3. Predicted Changes in Lipoprotein Values Based on a Change in S_I or Fasting Insulin From the 25th to 75th Percentile, Adjusted for Age, Age Plus BMI, and Age Plus BMI Plus WHR: The IRAS

Parameter	Age	Age + BMI	Age + BMI + WHR	*P* for Ethnicity × S_I or Ethnicity × Insulin
Triglycerides (mg/dL)				
S_I	−17.8	−16.0	−11.8	.227
Insulin	21.9	19.8	15.6	.648
HDL cholesterol (mg/dL)				
S_I	3.5	3.0	2.2	.605
Insulin	−4.6	−3.6	−2.8	.701
LDL size (Å)				
S_I	1.1	1.1	0.9	.710
Insulin	−1.4	−1.3	−1.1	.580

NOTE. for S_I, 25th percentile = 0.90 and 75th percentile = 2.91; fasting insulin, 25th percentile = 9.0 and 75th percentile = 19.0; analyses performed on log_e-transformed values. For statistical comparison, see Table 2.

There is evidence from animal studies that smaller VLDLs are converted to small LDLs,[52] and humans who are treated with simvastatin have more dense LDL in association with decreased synthesis of larger VLDL.[53] Alternatively, high levels of triglyceride-bearing lipoproteins may serve as acceptors for cholesterol esters and other constituents from LDL in exchange for triglyceride; this process is mediated by lipid transfer proteins.[54] If this occurs, and the triglycerides in LDL particles are removed by the action of lipoprotein lipase or hepatic triglyceride lipase, lipid-poor, protein-rich, dense LDL particles would result.

Of interest is the observation in the data set that the relationships between S_I and lipoproteins were independent of WHR. Thus, this measure of central obesity did not account for the link between insulin resistance or hyperinsulinemia and dyslipidemia. It has been suggested that the link between insulin resistance and dyslipidemia is entirely due to differences in abdominal obesity.[55] The present data suggest this is not the case.

Finally, it must be emphasized that the study participants do not represent a population-based sample in any of the three ethnic groups. Participants were recruited to represent a range of glucose intolerance even among the nondiabetic groups. Thus, the cohort was enriched in individuals with insulin resistance, as shown by the mean fasting insulin levels and values for body fat distribution; the results of the direct measures of insulin resistance have been reported previously[12] and show a high degree of insulin resistance in all three racial groups.

As noted by Haffner et al,[12] a possible limitation of the IRAS is the use of an insulin assay that cross-reacts with proinsulin. Porte[56] suggests that elevated proinsulin may be a marker of impaired β-cell function and, with other researchers,[57-59] confirms that proinsulin is disproportionately elevated in type II diabetes. Proinsulin also may be elevated with impaired glucose tolerance.[57,60]

In attempting to examine the relationships individually in each gender/ethnic group, relatively few subjects were available. This, along with the narrow range of insulin action, would explain why some of the gender/ethnic-specific trends did not reach statistical significance. When data from all gender/ethnic groups were combined, it became clear that the changes in triglycerides, HDL, and LDL size in comparing upper and lower quartiles of S_I were highly significant and not much diminished by adjustment for BMI or body fat distribution. This underlines the fundamental relationship between insulin resistance and lipoprotein metabolism independent of the other metabolic changes associated with insulin resistance. The changes in triglycerides, HDL, and LDL size for upper and lower quartiles of fasting insulin were similar to those observed for S_I, confirming that in population studies of nondiabetics, fasting insulin is a reliable indicator of insulin resistance when examining lipoprotein changes.

In summary, the results of the study strongly confirm that dyslipidemia is a prominent feature in individuals with insulin resistance in all ethnic groups studied. This dyslipidemia includes high VLDL, low HDL, and abnormal LDL composition. Strategies to aggressively control this dyslipidemia will be important in insulin-resistant individuals. The treatment options include exercise and weight loss; some pharmacologic agents such as thiazolidenediones or angiotensin-converting enzyme inhibitors may also prove beneficial.

REFERENCES

1. Reaven GM, Lerner RL, Stern MP, et al: Role of insulin in endogenous hypertriglyceridemia. J Clin Invest 46:1756-1767, 1967
2. Olefsky JM, Reaven GM: Decreased insulin binding to lymphocytes from diabetic subjects. J Clin Invest 54:1323-1328, 1974
3. Abbott WGH, Lillioja S, Young AA, et al: Relationships between plasma lipoprotein concentrations and insulin action in an obese hyperinsulinemic population. Diabetes 36:897-904, 1987
4. Garg AJ, Helderman H, Koffler M, et al: Relationship between lipoprotein levels and in vivo insulin action in normal young white men. Metabolism 37:982-987, 1988
5. Laakso M, Sarlund H, Mykkanen L: Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance. Arteriosclerosis 10:223-231, 1990
6. Godsland IF, Crook D, Walton C, et al: Influence of insulin resistance, secretion, and clearance on serum cholesterol, triglycerides, lipoprotein cholesterol, and blood pressure in healthy men. Arterioscler Thromb 12:1030-1035, 1992
7. Reaven GM, Chen YDI, Jeppesen J, et al: Insulin resistance and hyperinsulinemia in individuals with small dense low density lipoprotein particles. J Clin Invest 92:141-146, 1993
8. Austin MA, Selby JV: LDL subclass phenotypes and the risk factors of the insulin resistance syndrome. Int J Obes Relat Metab Disord 19:S22-S26, 1995 (suppl 1)
9. Wagenkneckt LE, Mayer EJ, Rewers M, et al: The Insulin Resistance Atherosclerosis Study (IRAS). Objectives, design and recruitment results. Ann Epidemiol 5:464-471, 1995
10. Hamman RF, Marshall JA, Baxter J, et al: Methods and prevalence of non–insulin dependent diabetes mellitus in a biethnic Colorado population: The San Luis Valley Diabetes Study. Am J Epidemiol 129:295-311, 1989
11. Stern MP, Rosenthal M, Haffner SM, et al: Sex difference in the effects of sociocultural status on diabetes and cardiovascular risk factors in Mexican Americans: The San Antonio Heart Study. Am J Epidemiol 120:834-851, 1984
12. Haffner SM, D'Agostino R Jr, Saad MF, et al: Increased insulin resistance and insulin secretion in nondiabetic African Americans and Hispanics compared with non-Hispanic whites: The Insulin Resistance Atherosclerosis Study. Diabetes 45:742-748, 1996
13. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. Endocr Rev 6:45-86, 1985
14. World Health Organization: Diabetes mellitus: Report of a WHO study group. World Health Org Tech Rep Ser 727; 1985
15. Bergman RN, Ider YZ, Bowden CR: Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667-E677, 1979
16. Bergman RN, Prager R, Volund A: Equivalence of the insulin sensitivity index in man derived by the minimal model and the euglycemic glucose clamp. J Clin Invest 79:790-800, 1987
17. Welch S, Gebhart SSP, Bergman RN, et al: Minimal model analysis of intravenous glucose tolerance test derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab 71:1508-1518, 1990
18. Howard G, O'Leary DH, Zaccaro D, et al: Insulin sensitivity and atherosclerosis. Circulation 93:1809-1817, 1996
19. Saad MF, Steil GM, Kades WW, et al: Differences between the tolbutamide-boosted and the insulin-modified minimal model protocols. Diabetes 46:1167-1171, 1997
20. Steil GM, Volund A, Kahn SE, et al: Reduced sample number for

calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. Diabetes 42:250-256, 1993

21. Herbert V, Lau K, Gottlieb C, et al: Coated charcoal immunoassay of insulin. J Clin Endocrinol Metab 25:1375-1384, 1965

22. Pacini G, Bergman RN: MINMOD: A computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed 23:113-122, 1986

23. Robbins DC, Welty TK, Wang WY, et al: Plasma lipids and lipoprotein concentrations among American Indians: Comparison with the US population. Curr Opin Lipidol 7:188-195, 1996

24. Krauss RM, Burke DJ: Identification of multiple subclasses of plasma low density lipoproteins in normal humans. J Lipid Res 23:97-104, 1982

25. Neter J, Wasserman W, Kutner MH: Applied Linear Statistical Models (ed 3). Homewood, IL, Richard D. Irwin, 1990

26. SAS Institute: SAS/STAT User's Guide, version 6, vol 2 (ed 4). Cary, NC, SAS Institute, 1989

27. Orchard TJ, Becker DJ, Bates M, et al: Plasma insulin and lipoprotein concentrations: An atherogenic association? Am J Epidemiol 118:326-337, 1983

28. Howard BV, Knowler WC, Vasquez B, et al: Plasma and lipoprotein cholesterol and triglyceride in the Pima Indian population. Arteriosclerosis 4:462-471, 1984

29. Cambien F, Warnet JM, Eschwege E, et al: Body mass, blood pressure, glucose, and lipids: Does plasma insulin explain their relationships? Arteriosclerosis 7:187-202, 1987

30. Donahue RP, Orchard TJ, Becker DJ, et al: Sex differences in the coronary heart disease risk profile: A possible role for insulin. Am J Epidemiol 125:650-657, 1987

31. Haffner SM, Fing D, Hazuda HP, et al: Hyperinsulinemia, upper body adiposity, and cardiovascular risk factors in non-diabetics. Metabolism 37:338-345, 1988

32. Burchfiel CM, Hammon RF, Marshall JA, et al: Cardiovascular risk factors and impaired glucose tolerance: The San Luis Valley Diabetes Study. Am J Epidemiol 131:57-70, 1990

33. McKeigue PM, Miller GJ, Marmot MG: Coronary heart disease in South Asians overseas: A review. J Clin Epidemiol 42:597-609, 1989

34. Modan M, Halkin H, Lusky A, et al: Hyperinsulinemia is characterized by jointly disturbed plasma VLDL, LDL, and HDL levels. Arteriosclerosis 8:227-236, 1988

35. Zavaroni I, Dall'Anglio E, Alpi O, et al: Evidence for an independent relationship between plasma insulin and concentration of high density lipoprotein cholesterol and triglyceride. Atherosclerosis 55:259-266, 1985

36. Manolio TA, Savage PJ, Burke GL, et al: Association of fasting insulin with blood pressure and lipids in young adults. Arteriosclerosis 10:430-436, 1990

37. Mykkanen L, Kuusisto J, Haffner SM, et al: Hyperinsulinemia predicts multiple atherogenic changes in lipoproteins in elderly subjects. Arterioscler Thromb 14:518-526, 1994

38. Reaven EP, Reaven GM: Mechanisms for development of diabetic hypertriglyceridemia in streptozotocin treated rats: Effect of diet and duration of insulin deficiency. J Clin Invest 54:167-178, 1974

39. Kissebah A: Insulin actions in vivo: Insulin and lipoprotein metabolism, in Alberti KGMM, Zimmet P, DeFronzo RA (eds): International Textbook of Diabetes Mellitus. Biochemistry and Pathophysiology. West Sussex, UK, 1992, pp 439-458

40. Sparks CE, Sparks JD, Bolognino M, et al: Insulin effects on apolipoprotein synthesis and secretion by primary cultures of rat hepatocytes. Metabolism 35:1128-1136, 1986

41. Howard BV: Lipoprotein metabolism in diabetes mellitus. J Lipid Res 28:613-628, 1987

42. Lewis GF, Uffelman KD, Szeto LW, et al: Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals. Diabetes 42:833-842, 1993

43. Peiris AN, Aiman EJ, Drucker WD, et al: The relative contributions of hepatic and peripheral tissue to insulin resistance in hyperandrogenic women. J Clin Endocrinol Metab 68:715-720, 1989

44. Fujioka S, Matsuzawa Y, Tokunage K, et al: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 36:54-59, 1987

45. Anderson AJ, Sobocinski KA, Freedman DS, et al: Body fat distribution, plasma lipids, and lipoproteins. Arteriosclerosis 8:88-94, 1988

46. Laws A, Hoen HM, Selby JV, et al: Differences in insulin suppression of free fatty acid levels by gender and glucose tolerance status: Relation to plasma triglyceride and apolipoprotein B concentrations. Arterioscler Thromb Vasc Biol 17:64-71, 1997

47. Pollare T, Vessby B, Lithell H: Lipoprotein lipase activity in skeletal muscle is related to insulin sensitivity. Arterioscler Thromb 11:1192-1203, 1991

48. Howard BV, Howard WJ: Dyslipidemia in non–insulin-dependent diabetes mellitus. Endocr Rev 15:263-274, 1993

49. Knudsen P, Eriksson J, Lahdenpera S, et al: Changes of lipolytic enzymes cluster with insulin resistance syndrome. Botnia Study Group. Diabetologia 38:344-350, 1995

50. Van Tol A, Ligtenberg JJ, Riemens SC, et al: Lowering of plasma phospholipid transfer protein activity by acute hyperglycaemia-induced hyperinsulinaemia in healthy men. Scand J Clin Lab Invest 57:147-157, 1997

51. Dullaart RP, Sluiter WJ, Dikkeschei LD, et al: Effect of adiposity on plasma lipid transfer protein activities: A possible link between insulin resistance and high density lipoprotein metabolism. Eur J Clin Invest 24:188-194, 1994

52. Shames DM, Yamada N, Havel RJ: Metabolism of apoB-100 in lipoproteins separated by density gradient ultracentrifugation in normal and Watanabe heritable hyperlipidemic rabbits. J Lipid Res 31:753-762, 1990

53. Gaw A, Packard CJ, Murray EF, et al: Effects of simvastatin on apoB metabolism and LDL subfraction distribution. Arterioscler Thromb 12:170-189, 1993

54. Deckelbaum RJ, Granot E, Oschry Y, et al: Plasma triglyceride determines structure-composition in low and high density lipoproteins. Arteriosclerosis 4:225-231, 1984

55. Després J-P, Allard C, Tremblay A, et al: Evidence for a regional component of body fatness in the association with serum lipids in men and women. Metabolism 34:967-973, 1985

56. Porte D: Banting Lecture 1990: β Cells in type II diabetes mellitus. Diabetes 40:166-180, 1991

57. Haffner SM, Bowsher RR, Mykkanen L, et al: Proinsulin and specific insulin concentration in high and low risk populations for non–insulin dependent diabetes mellitus. Diabetes 43:1490-1493, 1994

58. Ward WK, LaCava EC, Paquette TL, et al: Disproportionate elevation of immunoreactive proinsulin in type II (non–insulin dependent) diabetes mellitus and in experimental insulin resistance. Diabetologia 30:698-702, 1987

59. Yoshioka N, Kuzuya T, Matsuda A, et al: Serum proinsulin levels at fasting and after oral glucose load in patients with type II (non–insulin dependent) diabetes mellitus. Diabetologia 31:355-360, 1988

60. Davies MJ, Rayman G, Gray IP, et al: Insulin deficiency and increased plasma concentrations of intact and 32/33 split proinsulin in subjects with impaired glucose tolerance. Diabet Med 10:313-320, 1993