Insulin Resistance and Fat Patterning with Aging: Relationship to Metabolic Risk Factors for Cardiovascular Disease

William T. Cefalu, Sandra Werbel, Audrey D. Bell-Farrow, James G. Terry, Zhong Q. Wang, Emmanuel C. Opara, Timothy Morgan, William H. Hinson, and John R. Crouse III

Both insulin resistance and abdominal fat patterning are related to aging, and have been related to cardiovascular disease (CVD) risk factors such as dyslipidemia and hypertension. However, previous studies have not used direct methods to quantify the independent strength of the association of each of these two putative primary factors with metabolic outcomes. We quantified overall obesity by the body mass index (BMI) and used a previously validated magnetic resonance imaging (MRI) method to quantify abdominal fat in 63 healthy nondiabetic individuals aged 22 to 83 years. We also measured the glucose and insulin response to an oral glucose tolerance test and the insulin sensitivity ([S_I] by modified minimal model analysis). Body fat patterning was evaluated by the waist to hip ratio (WHR) and by MRI, which allowed direct measurement of subcutaneous (SCF) and intraabdominal (IAF) fat depots at the umbilicus in these subjects. These independent parameters were related to risk factors for CVD (blood pressure, lipids, and lipoproteins) and to plasma concentrations of free fatty acids (FFAs). Measures of overall obesity (BMI), total fat [TF], and/or SCF measured at the abdomen by MRI), glucose/insulin metabolism and S_I, and central fat patterning (WHR or IAF measured by MRI) were correlated with mean arterial pressure (MAP), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels in univariate analysis and after controlling for age and gender. An index of central fat patterning (WHR) added to the informativeness of the insulin area under the curve (IAUC) in explaining 24% of the variability in plasma TG concentration, but measures of overall obesity were not independently related. Both the BMI and TF contributed to the IAUC in explaining 32% to 34% of the variability in MAP, but central fat patterning was not independently related. No index of overall obesity, fat patterning, glucose/insulin metabolism, and/or S_I, was independently related to the plasma concentration of HDL-C after controlling for any one of the other two. Direct measurement of glucose/insulin metabolism and S_I, as well as fat patterning, provides information on their relative associations with CVD risk factors. The measures of glucose/insulin metabolism and S_I were more consistently related to dyslipidemia and hypertension than were the overall obesity and fat patterning in this healthy population.

INSULIN RESISTANCE is a characteristic feature of the aging process.[1,2] However, recent evidence suggests that body fat distribution, particularly central obesity, rather than aging per se is the major clinical factor contributing to the insulin resistance observed with age.[3,4] In addition, we recently quantified glucose/insulin metabolism and insulin sensitivity (S_I) and measured specific abdominal fat depots by magnetic resonance imaging (MRI) in a normal, healthy population to evaluate the association of S_I with fat distribution and the association of both of these with age.[5] These data showed strong correlations of S_I with intraabdominal fat (IAF) and of IAF with age in the group as a whole and in men and women separately. Specifically, the data demonstrated that IAF is a major clinical parameter contributing to the insulin resistance of aging: IAF accounted for over 50% of the variance in S_I, whereas age per se was not associated with S_I, in this population of healthy, weight-stable individuals.

Reaven et al[6] and Laakso[7] have recently reviewed the extensive literature that describes associations between plasma concentrations of insulin and glucose, indices of S_I, and other risk factors for cardiovascular disease (CVD) such as hypertension and dyslipidemia. Despres[8] and Matsuzawa et al[9] have similarly reviewed the associations of fat patterning with these same CVD risk factors. However, these putative primary variables (glucose/insulin metabolism, S_I, and central fat patterning) are correlated with one another,[5,10-14] and several investigators have evaluated the associations for measures of both glucose/insulin metabolism and S_I and fat patterning with these CVD risk factors. But these previous studies tend to be characterized by indirect measures of both glucose metabolism and fat patterning (eg, plasma concentrations of glucose and insulin, insulin area under the curve [IAUC], glucose area under the curve [GAUC], skinfold ratios, and waist to hip ratio [WHR]),[15-20] by direct measures of glucose metabolism (frequently sampled intravenous glucose tolerance test and steady-state plasma glucose levels) but indirect measures of fat patterning,[21-27] or by direct measures of fat patterning (computed tomography or MRI to quantify IAF) and indirect measures of glucose metabolism.[28-31] The relative influence of both S_i and fat patterning when quantified by direct measurement of both is unknown. For this reason, we evaluated the associations of S_i as measured by the frequently sampled intravenous glucose tolerance test[32] and fat patterning as measured by a validated MRI method[33] with lipids and lipoproteins, blood pressure, and lipoprotein(a) [Lp(a)] in a healthy population chosen for a wide age range but with a fixed level of obesity.

SUBJECTS AND METHODS

The study population has been described previously,[5] and consisted of 63 healthy individuals aged 23 to 83 years (18 men and 45 women).

From the Departments of Internal Medicine, Public Health Sciences, and Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem; and the Department of Surgical Science, Duke University Medical Center, Durham, NC.

Submitted April 16, 1997; accepted August 3, 1997.

Supported in part by US Public Health Service Grants No. AG-00578 (W.T.C.) and by the General Clinical Research Center of the Bowman Gray School of Medicine (M01-RR07122).

Address reprint requests to William T. Cefalu, MD, Bowman Gray School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1047.

0026-0495/98/4704-0007$03.00/0

Participants provided written informed consent and were interviewed for demographic data and information documenting eligibility. All subjects were fully ambulatory and normally active and took no medications known to affect glucose metabolism, blood pressure, or lipids. Only healthy individuals were admitted to the study as documented by history, electrocardiogram, complete blood cell count, routine blood and urine chemistry, and thyroid function tests. An equal number of subjects in each decade were chosen with greater than 125% and less than 125% ideal body weight (1953 Metropolitan Life Table). This selection strategy yielded a participant population that was, on average, moderately obese (body mass index [BMI], 29 ± 5 kg/m^2).

Quantification of Obesity and Fat Patterning

The BMI was calculated as body weight in kilograms divided by height in meters squared. The WHR was measured as the ratio of the minimal circumference of the abdomen to the circumference of the buttocks at the maximal gluteal protuberance.[34]

The fat mass at the umbilicus was quantified using a previously validated MRI technique[33] first described by Seidell et al.[35] The imaging parameters were as follows: TI = 300 milliseconds, TR = 833 milliseconds, and TE = 30 milliseconds. A 256 × 256 image matrix was acquired with two signals averaged. The field of view varied with individual patient size. According to the MRI protocol, the inversion recovery time is selected so that the expected signal for muscle tissue will be at zero crossing, thus producing no signal. Since the spin-lattice time of muscle is much longer than that of adipose tissue, the fat signal recovers substantially with a relatively long signal.

After obtaining longitudinal and cross-sectional scout images from each participant, the umbilicus was located and a set of four 10-mm thick slices were obtained, with the third slice positioned at the umbilicus (third lumbar vertebra) and 5 mm between slices. This section was used to quantify fat areas. This single slice at the umbilicus is highly correlated with the mean of all four slices (r = .985, N = 158, data not shown.[33])

Oral Glucose Tolerance Test

Glucose tolerance was determined for all subjects using a 75-g oral glucose tolerance test (World Health Organization criteria) performed after a 12-hour fast. Blood samples for determination of glucose and insulin were taken before and 30, 60, 120, and 180 minutes after glucose ingestion. Plasma glucose levels were measured by a glucose oxidase method (Beckman Instruments, Brea, CA), and insulin concentrations were measured by radioimmunoassay (Incstar, Stillwater, MN) as previously described.[5] Subjects demonstrating a diabetic response according to World Health Organization criteria were excluded from further study.

S_I

S_I was determined using the frequently sampled intravenous glucose tolerance test (minimal model[32]) with a modification using exogenous insulin administration.[36,37] Studies were initiated in the morning after an overnight fast. Two 18-gauge intravenous catheters were placed in each forearm and kept patent by a controlled flow of saline. Each line was equipped with a three-way stopcock. One line was used for intravenous administration of test substances, and the other for blood samples. Blood samples of 1 mL for insulin and glucose were drawn from the line at −15 minutes, −5 minutes, and immediately (0 minutes) before the glucose solution was injected. Glucose (300 mg/kg) was injected intravenously and the line was flushed with saline solution at 0 minutes. Blood samples of 1 mL were drawn at 2, 3, 4, 5, 8, 10, 12, 14, 16, 18, and 20 minutes. Regular insulin (Humulin Regular; Eli Lilly, Indianapolis, IN) was injected as an intravenous bolus of 0.03 U/kg at 20 minutes. Blood sampling continued at 22, 24, 28, 32, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 minutes. Samples were centrifuged immediately, and the plasma was placed on ice. Glucose determinations were made immediately after centrifugation using the glucose oxidase method on a Beckman Glucose Analyzer (intraassay coefficient of variation, 2%). Insulin was assayed within 1 week from frozen plasma by radioimmunoassay (Incstar; intraassay coefficient of variation, <5%). At each time point, glucose and insulin were determined in duplicate. S_I and glucose effectiveness were determined from the minimal model as previously described.

Plasma Concentrations of Lipids and Lipoproteins

Plasma concentrations of lipids and lipoproteins were evaluated in the Lipid Analytic Laboratory at Bowman Gray School of Medicine. This laboratory has been standardized according to the Centers for Disease Control, and Lipid Research Clinics methods were used.[38] After measuring total cholesterol (TC) and triglyceride (TG) levels in the whole plasma, the apolipoprotein B–containing lipoproteins were precipitated with heparin manganese and the supernatant high-density lipoprotein cholesterol (HDL-C) level was measured. Low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald formula as previously described.[39] The range of TG levels for this study was 40 to 433 mg/dL. The Lp(a) level was measured with the Macra enzyme-linked immunoassay (Strategic Diagnostics, Newark, DE). The

Table 1. Baseline Characteristics

Characteristic	Men (n = 18)		Women (n = 45)		All Subjects		P
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Age (yr)	49 ± 17	25-83	54 ± 18	22-83	53 ± 18	22-83	.32
Weight (kg)	92 ± 17	72-132	79 ± 16	46-119	83 ± 17	46-132	.01
MAP (mm Hg)	99 ± 10	84-117	97 ± 10	75-117	98 ± 10	75-117	.39
TC (mg/dL)	184 ± 30	139-251	200 ± 37	136-298	196 ± 35	136-298	.10
TG (mg/dL)	157 ± 82	64-372	143 ± 77	40-433	147 ± 78	40-433	.55
LDL-C (mg/dL)	112 ± 31	65-183	121 ± 34	73-224	119 ± 33	65-224	.36
HDL-C (mg/dL)	40 ± 10	24-64	51 ± 13	28-89	48 ± 13	24-89	<.01
Lp(a) (mg/dL)	22 ± 9	1-121	14 ± 11	1-45	16.5 ± 18	1-121	.29
Glucose (mg/dL)	88.7 ± 13.5	70-122	81.2 ± 11.2	62-122	83.3 ± 12.3	62-122	.06
BMI	28 ± 5	20-40	29 ± 6	18-45	29 ± 5	18-45	.63
WHR	.94 ± .08	.81-1.13	.90 ± .10	.69-1.05	.91 ± .10	.69-1.13	.11
TF (cm^2)	422 ± 163	252-813	509 ± 169	183-933	485 ± 171	183-933	.07
IAF (cm^2)	108 ± 52	40-214	114 ± 56	22-279	113 ± 54	22-279	.73
SCF (cm^2)	292 ± 121	163-688	396 ± 147	134-834	367 ± 147	136-834	.01
GAUC	1,447 ± 446	708-2,328	1,433 ± 264	871-2,021	1,437 ± 323	708-2,328	.90
IAUC	621 ± 558	99-2,241	685 ± 318	216-1,651	667 ± 397	99-2,241	.65
S_I	4.3 ± 3.5	.2-12	4.1 ± 2.3	.2-11.3	4.2 ± 2.7	.2-12	.91

assay procedure was performed as described by the manufacturer using 10 μL plasma that had been stored at −80°C and was not previously thawed. Intraassay and interassay coefficients of variation were each less than 7%. Samples were assayed in duplicate. Lp(a) concentrations less than 1 mg/dL were considered to be 1 mg/dL, whereas those greater than 80 mg/dL were diluted and repeated as recommended by manufacturer.

Free Fatty Acids

Plasma free fatty acid (FFA) levels were determined spectrophotometrically (Wako Kit #990-75401; Wako Pure Chemical Industries, Richmond, VA). Samples were frozen at −70°C until analysis.

Mean Arterial Pressure

Mean arterial pressure (MAP) was determined on all subjects. Three readings were taken over a 15-minute period after the subject had rested for 15 minutes in the sitting position. These readings were averaged for analysis. MAP was determined as one third pulse pressure.

Statistical Analysis

Comparison of baseline characteristics between men and women was performed using a *t* test. Pearson product-moment correlations were used to assess the correlation between measures, and all-possible-subset multiple regression analysis was used to select and test the best model with factors that had a significant independent effect.

RESULTS

Table 1 presents demographic characteristics and descriptive statistics for the 63 individuals who volunteered for this study. The mean age of the participants was 53 years (range, 22 to 83). The BMI of the men and women was similar and had a similar range in accordance with our selection strategies. Women had more subcutaneous fat (SCF) than men; cross-sectional total fat (TF) at the umbilicus was nonsignificantly greater in women versus men, and the WHR was nonsignificantly higher in men versus women. The women had higher plasma concentrations of HDL-C than the men. Other major risk factors including MAP, plasma TG and LDL-C, IAF, GAUC, IAUC, and S_I were similar between men and women.

Figure 1 shows the mean values for MAP, HDL-C, and IAF at each quartile of S_I; Fig 2 similarly identifies the mean values for MAP, HDL-C, and S_I at each quartile of IAF. A graded response of risk factors to both S_I and IAF is demonstrated.

Table 2 presents unadjusted correlations for the measures of obesity (BMI and MRI-determined TF and SCF), central fat patterning (anthropometrically ascertained WHR and MRI-determined IAF), and glucose/insulin metabolism (GAUC and IAUC) and S_I with MAP and plasma TC, LDL-C, HDL-C, TG, Lp(a), and FFA. For the group as a whole, only age was significantly correlated with LDL-C. Indices of obesity (most consistently BMI), central fat patterning (both WHR and IAF), and glucose/insulin metabolism and S_i were related to MAP and to plasma TG and HDL-C. The GAUC was inversely related to Lp(a), and the IAUC was related to plasma FFA concentrations. For men, the indices of glucose/insulin metabolism and S_I were related to MAP and plasma TG and HDL-C. Indices of overall obesity (BMI and TF) were additionally related to plasma TG, while central fat patterning (both WHR and IAF) was additionally related only to HDL-C. In women, indices of glucose/insulin metabolism and S_I were also related to blood pressure and, to a lesser extent, plasma TG and HDL-C. In addition, the indices of overall obesity (BMI and MRI-derived TF and SCF)

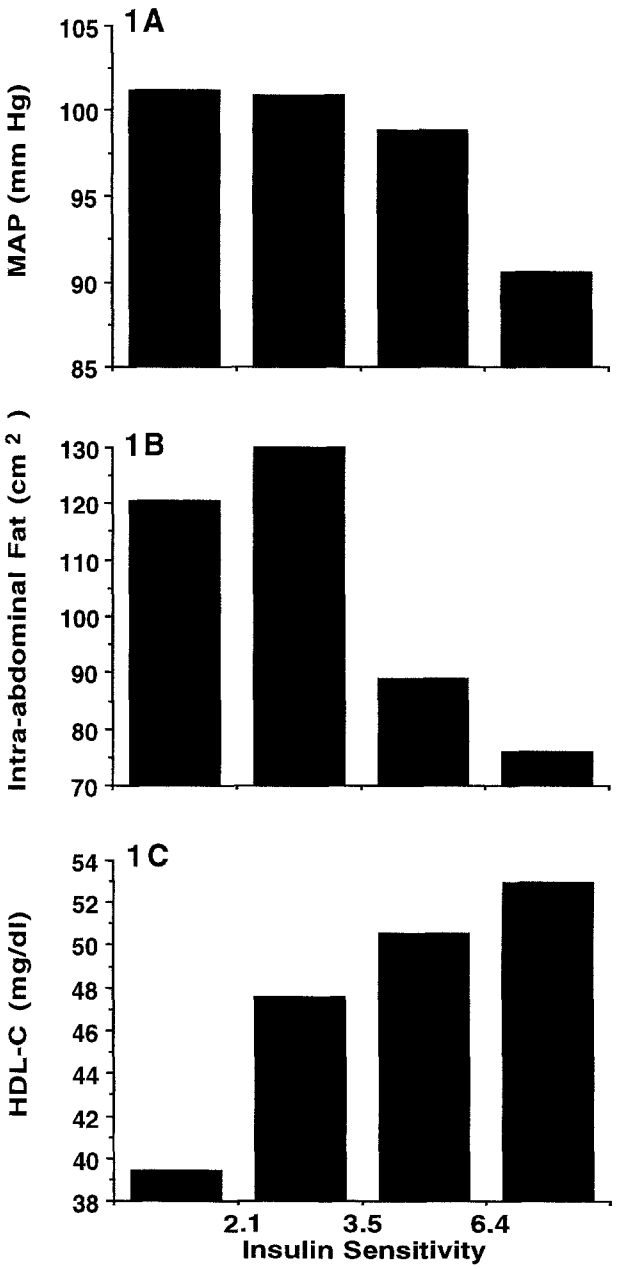

Fig 1. Mean MAP (A), IAF (B), and HDL-C (C) at each quartile of S_I ($\times 10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot mL$).

were related to MAP and the BMI was strongly correlated with TC. Both the MRI-derived IAF and, to a lesser extent, the GAUC were related to Lp(a), whereas the IAUC was related to plasma FFA.

After controlling for age and gender, the indices of overall obesity, glucose/insulin metabolism and S_I, and central fat patterning (MRI-derived IAF) remained correlated with MAP in the group as a whole (Table 3). Age- and gender-adjusted measures of glucose/insulin metabolism and S_I remained strongly associated with TG and HDL-C, whereas obesity and central fat patterning were less consistently correlated with lipids. In men, the previously observed uncorrected correlations were essentially unchanged; in women, age correction reduced the strength of association of the GAUC and plasma TG.

Table 2. Unadjusted Correlations ($P < .05$)

Parameter	MAP	TC	TG	LDL-C	HDL-C	Lp(a)	FFA
All subjects							
Age	.31 (.01)	.42 (.0006)		.29 (.02)			
BMI	.30 (.02)		.25 (.05)		−.26 (.04)		
TF	.38 (.0025)	.26 (.04)	.26 (.04)				
SCF	.24 (.06)	.34 (.0066)					
IAF	.43 (.0004)		.30 (.02)				
WHR	.31 (.013)		.40 (.001)		−.39 (0.0015)		
GAUC	.35 (.005)		.39 (.002)			−.30 (.002)	
IAUC	.37 (.003)		.36 (.004)				.33 (.009)
S_I	−.42 (.000)		−.33 (.009)		.35 (.005)		
Men ($P < .10$)							
Age							
BMI			.69 (.002)		−.41 (.09)		
TF			.62 (.008)				
SCF							
IAF					−.51 (.03)		
WHR					−.60 (.008)		
GAUC	.42 (.08)	.43 (.07)	.54 (.02)		−.51 (.03)		
IAUC	.48 (.04)		.58 (.01)		−.53 (.02)		
S_I	−.63 (.005)		−.62 (.006)		.55 (.02)		
Women ($P < .10$)							
Age	.36 (.01)	.51 (.0003)	.31 (.04)	.34 (.02)			
BMI	.33 (.02)	.51 (.0003)			−.27 (.07)		
TF	.41 (.004)			.25 (.10)			
SCF	.30 (.04)						
IAF	.48 (.001)		.38 (.01)			−.38 (.01)	
WHR	.32 (.03)	.31 (.04)	.41 (.005)		−.29 (.06)		
GAUC	.33 (.02)		.29 (.05)			−.27 (.08)	
IAUC	.35 (.02)						.32 (.03)
S_I	−.32 (.02)				.33 (.02)		

NOTE. Correlations are presented with P value for test of association in parentheses when the correlation was significant at the .05 level overall or at the .1 level for men and women separately.

Multivariable regression analysis for the dependent variable MAP identified a four-component model that included the significant independent predictors BMI and IAUC (age and gender were forced into all models) that explained 34% of the variance in blood pressure. In this model, age (partial $r^2 = .18$, $P < .001$), BMI (partial $r^2 = .10$, $P < .02$), and IAUC (partial $r^2 = .08$, $P < .03$) were significantly associated with MAP, whereas gender did not reach significance. One other such four-component model could be identified that contained the cross-sectional TF area by MRI in addition to the IAUC and explained 32% of the variance in MAP. The MRI-derived TF (partial $r^2 = .09$, $P < .03$), IAUC (partial $r^2 = .08$, $P < .03$), age (partial $r^2 = .11$, $P < .01$), and gender (partial $r^2 = .07$, $P < .05$) were all significantly associated with MAP in this model. Thus, the best models that could be constructed for MAP contained an index of overall obesity and one of insulin metabolism, but not an index of central fat patterning.

For plasma TG as the dependent variable, only one model could be identified that contained two independent variables in a model with age and gender. This model was constructed from the IAUC and WHR in addition to age and gender and explained 24% of the variability in plasma TG. The IAUC (partial $r^2 = .09$, $P < .02$) and WHR (partial $r^2 = .08$, $P < .03$) accounted for the majority of variance in the TG concentration, whereas age and gender each explained less than 2% of the variability in TG. No index of overall obesity entered the models tested after controlling for the IAUC and WHR.

For plasma HDL-C as the dependent variable, although the BMI, WHR, and S_I were significant predictors in models that included age and gender, no variable added significantly to the predictive power of any other. Models that included either the WHR or S_I were most informative, explaining approximately 29% of the variation in HDL-C. In one of these models, WHR (partial $r^2 = .17$, $P < .01$), gender (partial $r^2 = .08$, $P < .03$), and age (partial $r^2 = .07$, $P < .04$) all contributed significantly to the variation in HDL-C. In the other model, gender and S_I (partial $r^2 = .15$, $P < .01$ for each predictor) contributed equally to the variation in HDL-C and age was not significant.

Interactive effects between indices of obesity, central fat patterning, and glucose/insulin metabolism were not statistically significant for any of these models.

DISCUSSION

Interrelationships between CVD risk factors have been previously described, and a number of risk factors have been grouped under the common appellation of "syndrome X" including hypertension, dyslipidemia, insulin resistance, and abdominal obesity.[6] Two of the most important and possibly primary components of this syndrome, namely decreased S_I and central fat patterning, have each been related to CVD risk factors.[6-9] However, our group[5] and others[9-13] have previously noted strong correlations between fat patterning and S_I. In a recent population-based sample of 380 white subjects, the waist circumference, BMI, maximal aerobic capacity, and oral contra-

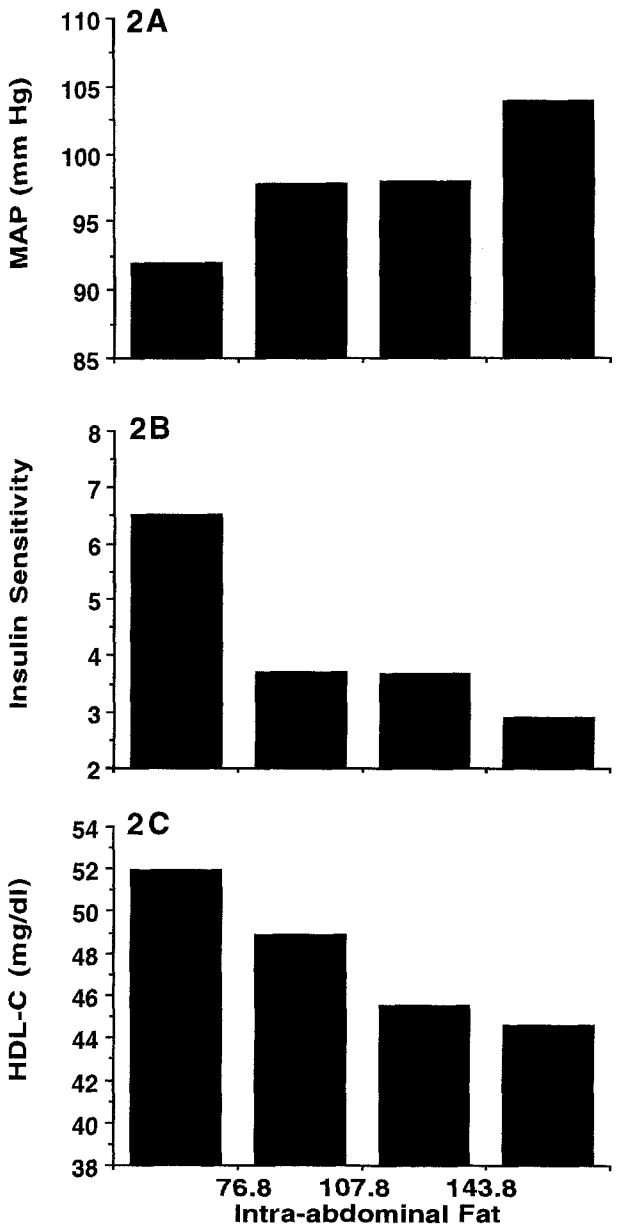

Fig 2. MAP (A), S_I ($\times 10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot mL$). (B), and HDL-C (C) at each quartile of IAF (cm^2).

ceptive use were the most import determinants of S_I.[40] Our previous analysis focused on healthy individuals of varying ages chosen for a predetermined range of BMI over each age group.[5] In that analysis, we observed a strong association of central fat patterning (MRI-derived IAF at the umbilicus) with S_I, as well as an association of IAF with age, but only a limited association of S_I with age.

To determine whether fat patterning or S_I was more important for explaining the variability in other CVD risk factors (lipids and lipoproteins and blood pressure), several investigators have attempted to relate both to CVD risk factors in the same population.[15-33] When indirect measures of both glucose metabolism (plasma insulin, IAUC, and GAUC) and fat patterning (WHR and skinfold ratios) were used, some investigators found both to be related to lipids and/or blood pressure.[16,17,19] Weinsier et al[20] found a stronger association of fat patterning, as compared with blood insulin, with blood pressure. Ward et al[18] found independent relations for indices of both central fat patterning (WHR) and glucose metabolism (serum insulin) with plasma TG, but a stronger association of insulin with plasma HDL-C, whereas Soler et al[15] found the WHR to be associated with plasma HDL-C and TG after adjustment for insulin concentration, but the converse was not true.

When investigators have used a combination of direct measures of glucose metabolism (eg, glucose uptake by euglycemic clamp or S_I by frequently sampled intravenous glucose tolerance test) and indirect measures of fat patterning (eg, WHR and x-ray absorptiometry), it has been the general experience that compared with fat patterning, S_I was more strongly correlated with blood pressure or left ventricular hypertrophy,[22,25,27] as well as lipids.[21,24,26] Mykkanen et al[23] attempted to ascertain the primary determinants of lipids in men and women: in men, the BMI was the primary determinant of plasma HDL-C, whereas S_I was the main determinant in women, and S_I was similarly the main determinant of plasma TG in both men and women.

When direct measures of central fat patterning (eg, IAF determined by computed tomography or MRI) were combined with indirect measures of glucose/insulin metabolism (eg, GAUC, IAUC, or plasma insulin), Johnson et al[30] and Boyko et al[28] both found plasma insulin to be more strongly correlated with blood pressure than directly measured IAF, whereas Peiris et al[31] found the opposite. On the other hand, Peiris et al[31] and Ferland et al[29] both evaluated associations of lipids with directly measured IAF and with insulin. Both studies found that IAF, a directly measured index of central fat patterning, was most strongly associated with lipids,[29,31] although Ferland et al[29] found an independent association of both IAF and the insulin level with the plasma TG concentration. To the best of our knowledge, there have been no previous investigations of the independent association of indices of fat patterning that include directly quantified IAF and directly quantified S_I with outcome variables such as blood pressure and plasma concentrations of lipids and lipoproteins.

In the current analysis, we were able to observe strong univariate correlations of measures of overall obesity (BMI and MRI-derived TF and SCF), central fat patterning (WHR and MRI-derived IAF), and glucose metabolism with blood pressure and plasma HDL-C and TG, in agreement with other investigators. After controlling for age and gender, these putative primary risk factors remained associated with MAP and with plasma HDL-C and TG. In multivariable models that included age and gender, indices of overall obesity (either BMI or MRI-derived TF at the umbilicus) and the IAUC were independently associated with blood pressure, with these models explaining 32% to 34% of the variation in MAP. The WHR and IAF, as measures of central fat patterning, were not independently related to MAP after controlling for the BMI, MRI-derived TF, or IAUC.

In a model that explained 24% of the variation in TG levels, central fat patterning (WHR) and the IAUC were independently related to plasma TG after controlling for age and gender. Measures of overall obesity (BMI and MRI-derived TF and SCF) were not independently important predictors of the TG

Table 3. Age/Gender-Adjusted Correlations ($P < .05$)

Parameter	MAP	TC	TG	LDL-C	HDL-C	Lp(a)	FFA
All subjects							
BMI	.42 (.001)		.32 (.01)		−.28 (.03)		
TF	.41 (.001)		.28 (.03)		−.25 (.05)		
SCF	.35 (.006)						
IAF	.34 (.008)				−.29 (.02)		
WHR			.36 (.007)		−.41 (.001)		
GAUC	.26 (.04)		.34 (.007)			−.29 (.03)	
IAUC	.40 (.001)		.37 (.003)		−.28 (.03)		.33 (.009)
S_I	−.43 (.000)		.33 (.01)		.39 (.002)		
Age-adjusted by men ($P < .10$)							
BMI			.70 (.002)		−.45 (.07)		
TF			.62 (.01)				
SCF							
IAF					−.44 (.09)		
WHR					−.60 (.01)		
GAUC		.49 (.05)	.70 (.002)		−.57 (.02)		
IAUC	.51 (.04)		.58 (.015)		−.54 (.02)		
S_I	−.61 (.009)		−.64 (.006)		.55 (.02)		
Age-adjusted by women ($P < .10$)							
BMI	.46 (.002)						
TF	.42 (.005)			.29 (.06)			
SCF	.36 (.02)	.26 (.08)					
IAF	.37 (.02)		.28 (.07)		−.25 (.09)	−.37 (.02)	
WHR			.35 (.02)		−.37 (.02)		
GAUC	.26 (.09)					−.26 (.10)	
IAUC	.36 (.02)						.32 (.04)
S_I	−.36 (.02)				.33 (.03)		

NOTE. Correlations are presented with P value for test of association in parentheses when the correlation was significant at the .05 level overall or at the .1 level for men and women separately.

concentration after controlling for the WHR or IAUC. Overall obesity (BMI and MRI-derived TF), central fat patterning (WHR and MRI-derived IAF), the IAUC, and S_I were associated with plasma HDL-C after controlling for age and gender, but none of these putative primary risk factors added to the strength of any other. However, models that contained age and gender, along with either the WHR or S_I, were most informative, each explaining 29% of the variation in HDL-C.

Haffner et al[41] have previously observed a positive but weak association of Lp(a) and S_I. In the current analysis, we similarly observed an inverse association between Lp(a) and the GAUC after controlling for age and gender. No association was observed between indices of fat patterning or obesity and Lp(a) in the population as a whole; however, Lp(a) was inversely associated with IAF in women.

One of the most important metabolic effects of insulin is to suppress the plasma FFA concentration.[42] Accordingly, we observed that the IAUC was related to plasma FFA, explaining 11% of the variation in FFA after controlling for age and gender. Measures of obesity and fat patterning were not significantly associated with FFA.

It is not possible to draw conclusions about the underlying pathogenesis of effects on CVD risk factors from these data. It is generally believed that obesity, particularly central fat patterning, modulates the association of decreased S_I, elevated blood pressure, and dyslipidemia in syndrome X.[6,43] It could be argued that central obesity leads to insulin resistance as a result of the relative increased sensitivity of centrally deposited IAF to sympathetic lipolytic activity and subsequent release of FFAs that inhibit glucose uptake, primarily in muscle,[44] inhibit insulin uptake in liver,[44] and stimulate insulin secretion by the pancreatic islets of Langerhans.[45] Thus, insulin resistance is postulated to result in part from central fat deposition, but it has also been argued that muscle insulin resistance may be the initiating factor ultimately resulting in accumulation of fat in the central area. Regardless, glucose/insulin metabolism may be more directly linked to CVD risk factors. Therefore, compared with central fat depots, indices of glucose/insulin metabolism and/or S_I may appear to be more strongly related to CVD risk factors. In this analysis, after controlling for age and gender, the IAUC was the most informative predictor of plasma TG, although the WHR entered the best subset regression model. Similarly, models with an age- and gender-adjusted IAUC along with either the BMI or MRI-derived TF as an index of overall obesity were the most informative predictors of MAP. The S_I and WHR were similarly associated with HDL-C after controlling for age and gender.

The present study is limited by the relatively small number of male participants. However, the use of precise, validated measures of obesity/fat distribution and glucose metabolism are among its strengths. The use of healthy participants with a broad range of age and obesity are also its strengths. Of interest for larger epidemiologic trials, the more easily measured IAUC, BMI, and WHR were as consistently related to outcome variables as S_I or MRI-derived IAF.

REFERENCES

1. Rowe JW, Minake KL, Pallotta JA, et al: Characterization of insulin resistance of aging. J Clin Invest 71:1581-1587, 1983
2. Fink RI, Koltermann OG, Griffin J, et al: Mechanism of insulin resistance in aging. J Clin Invest 71:1523-1535, 1983
3. Coon PJ, Rogus EM, Drinkwater D, et al: Role of body fat distribution in the decline in insulin sensitivity and glucose tolerance with age. J Clin Endocrinol Metab 75:1125-1132, 1992
4. Kohrt WM, Kirwan JP, Staten MA, et al: Insulin resistance in aging is related to abdominal obesity. Diabetes 42:273-281, 1993
5. Cefalu WT, Wang ZQ, Werbel S, et al: Contribution of visceral fat mass to the insulin resistance of aging. Metabolism 44:954-959, 1995
6. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities—The role of insulin resistance and the sympathoadrenal system. N Engl J Med 334:374-381, 1996
7. Laakso M: Insulin resistance and coronary heart disease. Curr Opin Lipidol 7:217-226, 1996
8. Despres J-P: Abdominal obesity as important component of insulin-resistance syndrome. Nutrition 9:452-459, 1993
9. Matsuzawa Y, Nakamura T, Shimomura I, et al: Pathophysiology and pathogenesis of visceral fat obesity. Obes Res 2:187S-194S, 1995 (suppl)
10. Park KS, Rhee BD, Lee KU, et al: Intra-abdominal fat is associated with decreased insulin sensitivity in healthy young men. Metabolism 40:600-603, 1991
11. Bonora E, Del Prato S, Bonadonna RC, et al: Total body fat content and fat topography are associated differently with in vivo glucose metabolism in nonobese and obese nondiabetic women. Diabetes 41:1151-1159, 1992
12. Zamboni M, Armellini F, Turcato E, et al: Relationship between visceral fat, steroid hormones and insulin sensitivity in premenopausal obese women. J Intern Med 236:521-527, 1994
13. Caprio S, Hyman LD, Limb C, et al: Central adiposity and its metabolic correlates in obese adolescent girls. Am J Physiol 269:E118-E126, 1995
14. Abate N, Garg A, Peshock RM, et al: Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest 96:88-98, 1995
15. Soler JT, Folsom AR, Kaye SA, et al: Associations of abdominal adiposity, fasting insulin, sex hormone binding globulin, and estrone with lipids and lipoproteins in post-menopausal women. Atherosclerosis 79:21-27, 1989
16. Ostlund RE, Staten M, Kohrt WM, et al: The ratio of waist-to-hip circumference, plasma insulin level, and glucose intolerance as independent predictors of the HDL_2 cholesterol level in older adults. N Engl J Med 322:229-234, 1990
17. Selby JV, Austin MA, Newman B, et al: LDL subclass phenotypes and the insulin resistance syndrome in women. Circulation 88:381-387, 1993
18. Ward KD, Sparrow D, Vokonas PS, et al: The relationships of abdominal obesity, hyperinsulinemia and saturated fat intake to serum lipid levels: The Normative Aging Study. Int J Obes 18:137-144, 1994
19. Burchfiel CM, Shetterly SM, Baxter J, et al: The roles of insulin, obesity, and fat distribution in the elevation of cardiovascular risk factors in impaired glucose tolerance. The San Luis Valley Diabetes Study. Am J Epidemiol 136:1101-1109, 1992
20. Weinsier RL, Norris DJ, Birch R, et al: Serum insulin and blood pressure in an obese population. I J Obes 10:11-17, 1986
21. Laws A, Reaven GM: Evidence for an independent relationship between insulin resistance and fasting plasma HDL-cholesterol, triglyceride and insulin concentrations. J Intern Med 231:25-30, 1992
22. Allemann Y, Horber FF, Colombo M, et al: Insulin sensitivity and body fat distribution in normotensive offspring of hypertensive parents. Lancet 341:327-331, 1993
23. Mykkanen L, Haffner SM, Ronnemaa T, et al: Is there a sex difference in the association of plasma insulin level and insulin sensitivity with serum lipids and lipoproteins? Metabolism 43:523-528, 1994
24. Walton C, Lees B, Crook D, et al: Relationships between insulin metabolism, serum lipid profile, body fat distribution and blood pressure in healthy men. Atherosclerosis 118:35-43, 1995
25. Lind L, Andersson P-E, Andren B, et al: Left ventricular hypertrophy in hypertension is associated with the insulin resistance metabolic syndrome. J Hypertens 13:433-438, 1995
26. Karhapaa P, Voutilainen E, Malkki M, et al: Obese men with type IIB hyperlipidemia are insulin resistant. Arterioscler Thromb 13:1469-1475, 1993
27. Pollare T, Lithell H, Berne C: Insulin resistance is a characteristic feature of primary hypertension independent of obesity. Metabolism 39:167-174, 1990
28. Boyko EJ, Leonetti DL, Bergstrom RW, et al: Visceral adiposity, fasting plasma insulin, and blood pressure in Japanese-Americans. Diabetes Care 18:174-181, 1995
29. Ferland M, Despres JP, Nadeau A, et al: Contribution of glucose tolerance and plasma insulin levels to the relationships between body fat distribution and plasma lipoprotein levels in women. Int J Obes 15:677-688, 1991
30. Johnson D, Prud'homme D, Despres JP, et al: Relation of abdominal obesity to hyperinsulinemia and high blood pressure in men. Int J Obes 16:881-890, 1992
31. Peiris AN, Sothmann MS, Hoffmann RG, et al: Adiposity, fat distribution, and cardiovascular risk. Ann Intern Med 110:867-872, 1989
32. Bergman RN: Toward physiological understanding of glucose tolerance—Minimal model approach. Diabetes 38:1512-1527, 1989
33. Terry JG, Hinson WH, Evans GW, et al: Evaluation of magnetic resonance imaging for quantification of intraabdominal fat in human beings by spin-echo and inversion-recovery protocols. Am J Clin Nutr 62:297-301, 1995
34. Thompson CJ, Ryu JE, Craven TE, et al: Central adipose distribution is related to coronary atherosclerosis. Arterioscler Thromb 11:327-333, 1991
35. Seidell JC, Bakker CJG, Van der Kooy K: Imaging techniques for measuring adipose tissue distribution—A comparison between computed tomography and 1.5 magnetic resonance. Am J Clin Nutr 51:953-957, 1990
36. Welch S, Gebhart SSP, Bergman RN, et al: Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetes subjects. J Clin Endocrinol Metab 71:1508-1518, 1990
37. Finegood DT, Hramiak IM, Dupre J: A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. J Clin Endocrinol Metab 70:1538-1549, 1990
38. Lipid Research Clinics: Manual I, DHEW No. (NIH) 75-628. Bethesda, MD, National Heart, Lung, and Blood Institute, 1974
39. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma without the use of preparative ultracentrifuge. Clin Chem 18:499-502, 1972
40. Clausen JO, Borch-Johnsen K, Ibsen H, et al: Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy caucasians. Analysis of the impact of gender, body fat, physical fitness, and life-style factors. J Clin Invest 98:1195-1209, 1996
41. Haffner SM, Karhapaa P, Rainwater DL, et al: Insulin sensitivity and Lp(a) concentrations in normoglycemic men. Diabetes Care 18:193-199, 1995

42. Reaven GM: Banting Lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

43. Depres JP: Dyslipidaemia and obesity. Baillieres Clin Endocrinol Metab 8:629-660, 1994

44. Defronzo RA: Lilly Lecture 1987. The triumvirate: β-Cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 37:667-687, 1988

45. Opara EC, Garfinkel M, Hubbard VS, et al: Effect of fatty acids on insulin release: Role of chain length and degree of unsaturation. Am J Physiol 266:E635-E639, 1994