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Metabolism Clinical and Experimental 57 (2008) 1190–1197
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Co-associations between insulin sensitivity and measures of liver function, subclinical inflammation, and hematology

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Received 20 June 2007; accepted 22 April 2008

Abstract

Clustering of risk factors for coronary heart disease and diabetes is well established, particularly in relation to insulin resistance. To determine whether evaluation of risk factor clustering will contribute to risk assessment, it is first necessary to discriminate co-association between risk factors from correlation. We undertook this in a large homogenous group, using a sophisticated measure of insulin sensitivity and a broad range of risk factors. Cross-sectional analysis of an occupational cohort using regression and factor analyses was performed. Subjects were 472 apparently healthy white men. The main outcome measures were insulin sensitivity, S_I, by minimal model analysis of the intravenous glucose tolerance test plus liver function and hematologic variables, including the inflammation indices, leukocyte count, and erythrocyte sedimentation rate. The S_I correlated independently with serum γ-glutamyl transferase (GGT), aspartate transaminase, and alkaline phosphatase activities; blood pressure; leukocyte count; and erythrocyte sedimentation rate ($P < .01$). On factor analysis, the factor that explained the greatest proportion of the variance (56.7%) included, in decreasing order of factor loading, triglycerides, S_I (negative), body mass index, high-density lipoprotein cholesterol (negative), insulin, uric acid, and GGT activity (loadings >0.40). Mean arterial pressure was not a feature (loading 0.29), neither were indices of subclinical inflammation. In apparently healthy men, blood pressure and indices of subclinical inflammation do not cluster with other insulin resistance–related risk factors, despite correlating with insulin sensitivity. In contrast, both GGT activity and uric acid concentrations correlated with insulin sensitivity and co-associated with insulin resistance–related risk factors and are therefore components of a true risk factor cluster.

Recognition that disturbances in a range of risk factors for coronary heart disease (CHD) cluster together has been growing for many years. Interest in such clustering comes from the possibility that evaluation of risk factor clusters in contrast to levels of individual risk factors may enhance prediction of CHD. To date, this has been found not to be the case [1,2]. However, the resolution of this issue is hindered by uncertainties over the validity of the risk factor cluster definitions that have been proposed [3,4].

Current controversies have their origins in the proposal of Reaven [5] that insulin resistance could provide the mechanistic basis for an adverse cluster of CHD risk factors. However, attention was diverted from a rigorous investigation of this concept by the difficulty of measuring insulin resistance in the clinical setting. The metabolic syndrome provided a more accessible alternative, with representative variables selected based on their intercorrelation and ease of measurement. However, the metabolic syndrome concept remains provisional [6]; and there will be further approaches to the definition and use of risk factor clustering, some or none of which may ultimately enhance risk evaluation. In the meantime, despite an excessive number of population-based correlation studies, the clustering behavior in individuals of CHD risk factors and measured insulin resistance (in contrast to plasma insulin concentrations) remains underresearched.

The distinction between correlation and clustering is important. There may be many different physiological and biochemical processes contributing to or affected by the whole-body insulin resistance that established techniques quantify, but risk factors may vary in the way they relate to these processes. For example, dyslipidemia and hypertension

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0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.04.010

may both be associated with insulin resistance; but processes underlying their associations could be shared or separate [7,8]. Evaluation of simple correlations will not discriminate which alternative predominates, whereas this can be achieved by an assessment of co-association. Co-association will be present when high or low levels of a particular combination of risk factors show a strong tendency to be present together in individuals.

Insulin resistance or hyperinsulinemia appears to be only a weak predictor of incident CHD, but evaluation of co-associations of insulin resistance and CHD risk factors might enhance risk assessment. In evaluating such co-association, the technique of factor analysis has been widely, albeit unevenly, applied [9]. There is evidence that measures of liver function, subclinical inflammation, and hematology are related to insulin sensitivity [10-12]; but to date, there appear to be no published investigations of the co-association of representative measures from each of these functional areas with measured insulin resistance and other insulin resistance–related risk factors, such as lipids and blood pressure. The present analysis, drawn from the Heart Disease and Diabetes Risk Factors in a Screened Cohort (HDDRISC) study, evaluates co-associations between insulin resistance, measured as insulin sensitivity, S_I, by minimal model analysis, and liver function and hematologic variables, including the subclinical inflammation-related variables serum globulin concentration, leukocyte or white blood cell count (WBC), and erythrocyte sedimentation rate (ESR).

1. Research design and methods

1.1. Design

The HDDRISC study is an open, occupational cohort study of metabolic risk factors for the development of CHD and diabetes. The study began in 1971 and derives from a company health program, in the course of which participants received a range of metabolic, clinical, and laboratory measurements. The present analysis concerns the 472 consecutively studied male recruits free of CHD and diabetes and taking no blood pressure–, lipid- or uric acid–lowering medications who between 1987 and 1995 underwent an intravenous glucose tolerance test (IVGTT). The study received local ethics committee approval, and each participant gave written informed consent.

1.2. Procedures

Participants fasted overnight (>12 hours) and refrained from cigarette smoking on the morning of their visit. Height and weight were measured; and a general medical history was taken, including details of exercise habits and of alcohol and tobacco consumption. After resting for 15 minutes in a semirecumbent position, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a mercury sphygmomanometer. Blood samples were taken from an indwelling cannula for routine biochemistry and hematology and for measurement of ESR, fasting plasma glucose and insulin, and serum lipid and lipoprotein concentrations. A sample was taken for a second measurement of glucose and insulin concentrations. All samples were kept on ice and separated within 1 hour of being taken. Routine biochemical variables were measured on the same day. Plasma samples for measurement of insulin were stored at −20°C. An intravenous glucose injection was then given (0.5 g glucose per kilogram of body weight as a 50% wt/vol solution of dextrose, given over 3 minutes) via the cannula in the opposite arm to the sampling arm. Blood samples (10 mL) were then taken at 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 minutes for measurement of plasma glucose and insulin.

1.3. Laboratory measurements

Plasma glucose and insulin, and serum total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol concentrations were measured as described previously [13]. Routine hematology included measurement of hemoglobin, hematocrit, and WBC. Erythrocyte sedimentation rate was measured by the Westergren method. Liver function tests included serum albumin, globulin, bilirubin, and uric acid concentrations; γ-glutamyl transferase (GGT), aspartate aminotransaminase (AST), and alkaline phosphatase (ALP) activities; as well as serum calcium and phosphate concentrations. Hematologic and biochemical measurements were made using routine laboratory methodology. Biochemical measurements were made on a Cobas Mira discrete clinical analyzer (Roche, Basel, Switzerland).

Quality control was monitored with pooled, frozen plasma samples and lyophilized sera and by participation in national schemes. Particular attention was given to maintaining long-term continuity of measurement with replicate assay of previously analyzed, frozen samples. Assay methodology did not change during the period of data acquisition for this analysis. Between-batch assay coefficients of variation were as follows: <2% for cholesterol and triglycerides; <3% for glucose, calcium, and phosphate; <4% for HDL cholesterol, urea, and GGT activity; <6% for insulin, uric acid, globulin, and albumin concentrations and ALP activity; <8% for bilirubin; and <9% for AST activity.

1.4. Intravenous glucose tolerance test modeling analysis

Insulin sensitivity, S_I, was determined using the minimal model of glucose disappearance [14]. Model identification was by nonlinear regression using the MLAB mathematical modeling package (Civilized Software, Bethesda, MD) implemented to maximize successful model identification [15]. The S_I quantifies insulin sensitivity as the fractional rate of clearance of the glucose distribution space per unit plasma insulin concentration. We have found that, in those free of diabetes, the relatively high glucose dose (0.5 g kg^{-1}) we use provides for a high rate of model identification without

augmentation of insulin concentrations by tolbutamide or insulin injection. Measures of S_I using this protocol correlate with those from the euglycemic clamp at $r = 0.92$ [16].

1.5. Data analysis

Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Fasting plasma glucose and insulin concentrations were expressed as the mean of the 2 fasting measurements. The IVGTT glucose tolerance was expressed as the k value (ie, the slope of the regression line for time and the natural log of the IVGTT glucose concentrations between 20 and 60 minutes). Statistical analysis used STATA 8 (Stata, College Station, TX). Measures were log transformed, as appropriate, to normalize their distributions. Univariate associations between insulin sensitivity and other variables were explored by Pearson correlation and linear regression analysis, and the independence of significant associations was confirmed by multiple linear regression.

Co-association of intercorrelated variables was detected by exploratory factor analysis [9]. Factor analysis supposes that where, in a population, a number of measured variables correlate with each other to varying degrees, this reflects the influence of a smaller number of underlying, unmeasured factors, which are expressed with varying intensity in the individuals of the population. Variability in each measured variable may then be considered in terms of separate components, each of which relates to a greater or lesser extent to each underlying factor. The strength of the relationship between a measured variable and each underlying factor is quantified in factor analysis by "factor loadings," which are equivalent to the correlation coefficients between the measured variable and each factor. Those measured variables that "load" onto a particular factor above a certain level (conventionally 0.40) may be considered to be co-associated.

The physiologic nature of the factor responsible for this co-association is suggested by the nature of the variables that load onto the factor. For example, if factor analysis distinguishes a factor on which age, blood pressure, and glucose concentrations all load positively with a loading of 0.40 or higher, that factor may be interpreted as embodying adverse aspects of the aging process. Individuals who express this factor with high intensity will be those in whom aging has been accompanied by markedly adverse changes in blood pressure and glucose homeostasis. Various procedures are available for factor analysis. In the present study, a principal-factors analysis followed by varimax rotation, as previously described for this cohort, was used [17]. Variables that correlated with S_I in univariate analysis at $P < .05$ were entered into the factor analysis. Blood pressure was entered into the analysis as mean arterial pressure—[(2 × DBP) + SBP]/3—to avoid the emergence of a single, noninformative factor comprising the 2 highly correlated blood pressure measurements [9]. For the same reason, blood hemoglobin concentration but not hematocrit was entered. The Pearson correlation between SBP and DBP was 0.76, and that between hemoglobin and hematocrit was 0.80. The next strongest correlation was between triglycerides and HDL cholesterol, with a correlation coefficient of −0.50. These 2 variables appeared to behave independently in factor analysis and were, therefore, not entered as a single representative variable; neither were any other pairs of variables, all of which correlated more weakly. Only factors with eigenvalues greater than 1 were considered for interpretation. Variables were considered to be features of a given factor if their loading on that factor was 0.40 or more, with loadings of 0.30 to 0.40 signifying borderline importance.

2. Results

Of the 472 individuals studied, 467 had IVGTT data that could be successfully analyzed using the minimal model (Table 1). Eighty percent were nonsmokers, 13% were light smokers, and 7% smoked 15 or more cigarettes per day; 8% took regular aerobic exercise, 46% took regular nonaerobic exercise, and 46% took no exercise; 15% drank little or no alcohol, 59% drank up to 28 U of alcohol per week, and 26%

Table 1
Study group characteristics and Pearson correlation coefficients (R) with insulin sensitivity, S_I

	Mean (SD)	Correlation with S_I
Age (y)	49.2 (10.0)	−0.11*
BMI (kg m^{-2})	25.6 (2.9)	−0.43‡
Insulin sensitivity, S_I[a, b] (min^{-1} mU^{-1} L mg^{-1} dL 10^4)	3.20 (−1.33, +2.31)	1.00
Fasting plasma glucose (mmol L^{-1})	5.34 (0.44)	−0.19‡
Fasting plasma insulin[a] (mU L^{-1})	6.8 (−3.9, +9.2)	−0.39‡
IVGTT k value[a] (min^{-1})	1.40 (−0.41, +0.58)	0.20‡
SBP (mm Hg)	124.0 (16.2)	−0.31‡
DBP (mm Hg)	78.1 (9.8)	−0.28‡
Total cholesterol (mmol L^{-1})	5.37 (0.90)	−0.17‡
Triglycerides[a] (mmol L^{-1})	1.10 (−0.48, +0.84)	−0.43‡
HDL cholesterol (mmol L^{-1})	1.30 (0.29)	0.26‡
LDL cholesterol (mmol L^{-1})	3.47 (0.83)	−0.07
Uric acid (μmol L^{-1})	338.1 (77.5)	−0.33‡
GGT (IU L^{-1})	26.3 (23.8)	−0.26‡
AST (IU L^{-1})	24.8 (9.3)	−0.20‡
ALP (IU L^{-1})	62.7 (16.9)	−0.21‡
Bilirubin (μmol L^{-1})	11.7 (5.2)	0.15†
Calcium (mmol L^{-1})	2.27 (0.12)	−0.01
Phosphate (mmol L^{-1})	1.05 (0.16)	0.10*
Albumin (g L^{-1})	44.6 (3.0)	−0.04
Globulin (g L^{-1})	21.7 (3.3)	−0.14†
WBC (10^9 L^{-1})	5.53 (1.77)	−0.12†
ESR (mm)	4.0 (4.7)	−0.19‡
Hemoglobin (g dL^{-1})	14.3 (0.87)	−0.13†
Hematocrit	0.42 (0.03)	−0.11*

Significances: *$P < .05$, †$P < .01$, and ‡$P < .001$.
[a] Mean and SD back-transformed from log-transformed data.
[b] n = 467 successful minimal model analyses.

drank more than 28 U of alcohol per week. Cigarette smoking and alcohol intake were not significantly correlated with S_I, but exercise was positively correlated ($r = 0.14$, $P = .002$).

Variables showing no evidence of significant association with S_I on univariate Pearson correlation analysis were LDL cholesterol, serum calcium, and albumin concentrations (Table 1). In relation to S_I, correlation coefficients of magnitude 0.19 or higher ($P < .0001$) were obtained for BMI; SBP; DBP; mean fasting glucose and insulin concentrations; IVGTT k value; fasting triglyceride, HDL cholesterol, and uric acid concentrations; ESR; and GGT, AST, and ALP activities. Coefficients of 0.16 to 0.19 ($P < .001$) were obtained for serum total cholesterol concentration; 0.12 to 0.16 ($P < .01$) for exercise habit, WBC, blood hemoglobin, and serum bilirubin and globulin concentrations; and 0.09 to 0.12 ($P < .05$) for age, hematocrit, and serum phosphate concentration.

For those variables that correlated significantly with S_I, multiple linear regression analysis was used to explore the independence of their relationships with S_I from age, BMI, cigarette smoking, alcohol intake, and exercise habit. The magnitude of the effect of age, BMI, cigarette smoking, alcohol intake, and exercise habit on relationships with S_I was assessed by comparing the regression coefficient in univariate regression analysis without these covariates with the regression coefficient in multiple linear regression analysis with covariates included (Table 2). Fasting plasma glucose, serum phosphate and hemoglobin concentration, and hematocrit ceased to be significantly associated with S_I after inclusion of age, BMI, cigarette smoking, alcohol intake, and exercise habit. Among liver function–related variables, S_I was a significant independent negative determinant of GGT, AST, and ALP activities and of uric acid concentrations and was an independent positive determinant of serum bilirubin concentration. Notably, although there was a positive relationship between GGT activity and alcohol consumption ($r = 0.23$, $P < .001$), the association between GGT activity and insulin sensitivity was independent of alcohol. Among inflammation-related variables, S_I was a significant independent negative determinant of serum globulin concentration, ESR, and WBC. Regression coefficients were reduced in magnitude by inclusion of age, BMI, cigarette smoking, alcohol intake, and exercise habit by 46% to 30% for DBP and SBP and total and HDL cholesterol and by 28% to 10% for fasting plasma insulin; serum uric acid, triglyceride, and bilirubin concentrations; and GGT and ALP activities.

On factor analysis, 2 factors with eigenvalues greater than 1 emerged (Table 3). The factor explaining the greatest proportion of the variance in the data (56.7%) incorporated, in decreasing order of factor loading, triglycerides, S_I (negative), BMI, fasting plasma insulin, serum HDL cholesterol concentration (negative), serum uric acid concentration, GGT activity, serum uric acid concentration, serum cholesterol concentration (borderline),

Table 2
Regression coefficients (change in dependent variable per unit change in log S_I) from linear regression analyses for insulin sensitivity, S_I, as a determinant of dependent variables showing a significant univariate correlation with S_I in Pearson correlation analysis (except age, BMI, and exercise habit): with S_I alone as a determinant and with S_I as determinant with BMI, cigarette smoking, alcohol intake, and exercise included as covariates

Dependent variable	Regression coefficient for S_I	
	S_I alone as a predictor	S_I and covariates
Fasting plasma glucose (mmol L^{-1})	−0.153 ‡	−0.065
Fasting plasma insulin * (mU L^{-1})	−0.618 ‡	−0.493 ‡
IVGTT k value * (min^{-1})	0.130 ‡	0.132 ‡
SBP (mm Hg)	−9.099 ‡	−5.636 ‡
DBP (mm Hg)	−5.126 ‡	−2.762 †
Total cholesterol (mmol L^{-1})	−0.276 ‡	−0.176 *
Triglycerides * (mmol L^{-1})	−0.448 ‡	−0.360 ‡
HDL cholesterol (mmol L^{-1})	0.141 ‡	0.097 ‡
Uric acid (μmol L^{-1})	−46.891 ‡	−33.839 ‡
GGT (IU L^{-1})	−11.501 ‡	−8.916 ‡
AST (IU L^{-1})	−3.481 ‡	−3.446 ‡
ALP (IU L^{-1})	−6.617 ‡	−5.754 ‡
Bilirubin (μmol L^{-1})	1.399 †	1.254 *
Phosphate (mmol L^{-1})	0.028 *	0.018
WBC (10^9 L^{-1})	−0.396 †	−0.489 †
ESR (mm)	−1.660 ‡	−1.594 ‡
Globulin (g L^{-1})	−0.840 †	−0.807 *
Hemoglobin (g dL^{-1})	−0.210 †	−0.161
Hematocrit	−0.006 *	−0.004

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

Table 3
Factor analysis in 467 men with insulin sensitivity, S_I

	Factor loadings with S_I	
	Factor 1	Factor 2
Age	−0.04	**0.52**
Insulin sensitivity, S_I	**−0.60**	−0.28
BMI	**0.58**	0.07
Exercise habit	−0.11	−0.17
Mean arterial pressure	0.29	**0.46**
Fasting plasma glucose	0.23	0.26
Fasting plasma insulin	**0.51**	−0.09
IVGTT k value	−0.02	**−0.48**
Cholesterol	0.32	0.08
Triglycerides	**0.74**	−0.03
HDL cholesterol	**−0.51**	0.25
Hemoglobin	0.32	−0.20
ESR	0.18	0.23
WBC	0.25	−0.04
Uric acid	**0.49**	0.12
Phosphate	−0.14	−0.01
ALP	0.29	0.24
Globulin	0.19	0.14
AST	0.18	0.34
Bilirubin	−0.09	−0.06
GGT	**0.46**	0.20
% Variance explained	56.7%	20.4%

Factors with eigenvalues greater than 1.0. Factor loadings greater than 0.4 are highlighted.

and blood hemoglobin concentration (borderline). The second factor (20.4% of the variance explained) incorporated age, IVGTT *k* value (negative), mean arterial pressure, and AST activity (borderline).

3. Discussion

Insulin sensitivity in this large, relatively homogenous group was independently associated with the following liver function–related measures: serum GGT, AST, and ALP activity and uric acid concentration (all negative) and bilirubin concentration (positive). It was also independently associated with SBP and DBP and the inflammation-related variables globulin, WBC, and ESR (all negative). However, on factor analysis, only high GGT activity and uric acid concentration co-associated with low insulin sensitivity and the other insulin resistance–related variables (ie, triglycerides, BMI, HDL cholesterol, and fasting insulin). Although correlated with insulin sensitivity, indices of inflammation were not part of this cluster; neither was blood pressure. These findings distinguish measures that genuinely co-associate from those that simply correlate (Fig. 1). The co-associated measures included insulin sensitivity and could contribute to the delineation of a rigorously defined insulin resistance–related risk factor cluster for evaluation as a risk factor for CHD or for type 2 diabetes mellitus [18,19]. Other risk factors considered here that correlate with insulin sensitivity may also be important for risk evaluation but not in the context of co-associated measures in a rigorously defined cluster.

We have previously reported the co-association of a more limited range of risk factors in relation to oral glucose tolerance test insulin concentrations as a surrogate index of insulin sensitivity [13,17,20] and have established in subgroup analyses that leptin [21] and several factors of the hemostatic system [22] co-associate with low insulin sensitivity and other insulin resistance–related risk factors. In contrast, homocysteine neither correlated nor co-associated with low insulin sensitivity [23]. The present analysis extends these earlier studies with a more than 4-fold increase in sample size and includes for the first time the full range of measures of liver function, inflammation, and hematology recorded in the HDDRISC study, in addition to measurement of insulin sensitivity by minimal model analysis.

Our findings strongly support the inclusion of uric acid and GGT activity in insulin resistance–related risk factor clustering, and the independent variation of these 2 measures with respect to insulin sensitivity and BMI is illustrated in Fig. 2. Measurement of serum uric acid concentrations has been a traditional component of the standard biochemical profile, and reports began to appear shortly after recognition of insulin resistance–related risk factor clustering that high levels of uric acid were one of its features [24]. γ-Glutamyl transferase is significantly related to known correlates of insulin resistance [25-28], but published information combining GGT activity and measured insulin sensitivity is very limited [29,30]. Our findings confirm a strong negative relationship between GGT activity and insulin sensitivity and demonstrate for the first time, we believe, that there is true co-association between GGT activity, low insulin sensitivity, and a range of other risk factors.

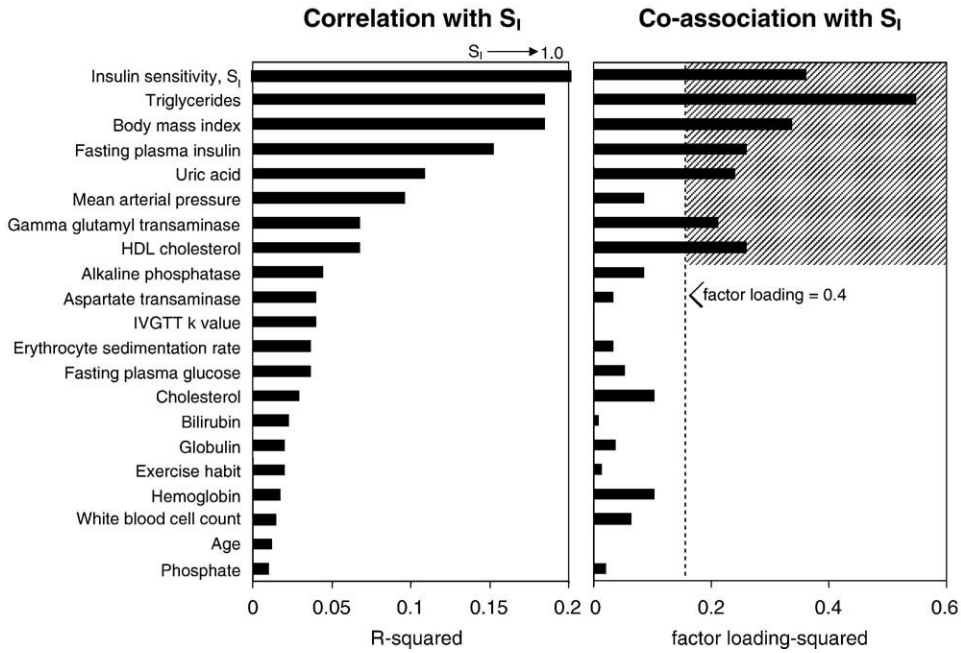

Fig. 1. Significant univariate correlates of insulin sensitivity, S_I, ordered according to the square of their correlation coefficient and compared with the square of their loading on factor 1. The hatched area discriminates those variables that loaded on factor 1 with a loading of higher than 0.4.

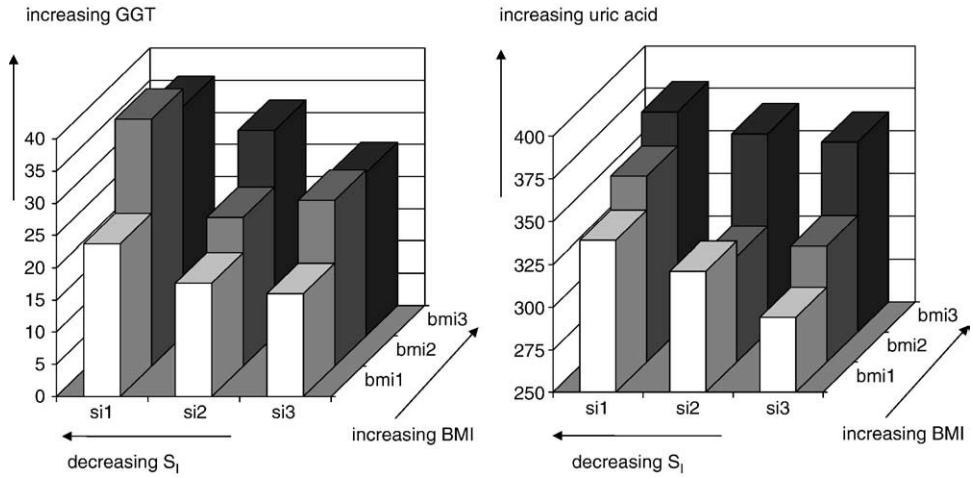

Fig. 2. Mean GGT activities and serum uric acid concentrations in tertiles of insulin sensitivity, S_I, and BMI in 467 apparently healthy men with insulin sensitivity measured by minimal model analysis.

The association between GGT activity, insulin resistance, and lipid measures suggests an involvement of fat deposition in the liver [10]. The GGT activity may, nevertheless, be raised in association with insulin resistance independently of hepatic fat deposition because, in contrast to AST and alanine aminotransferase activities, it shows little relationship with the severity of hepatic fat deposition [31]. γ-Glutamyl transferase differs from other liver enzymes in that it is widely distributed throughout the body and is induced by oxidative stress, possibly as an adaptive response whereby intracellular availability of the antioxidant glutathione is increased [32]. Increased GGT with increasing insulin resistance could, therefore, accord with links between insulin resistance and increased oxidative stress [33]. Variation in alanine aminotransferase activity has been widely explored in relation to insulin resistance [34,35] but was not measured in the full HDDRISC cohort.

A negative relationship between WBC and insulin sensitivity has been observed using a range of techniques for measurement of insulin sensitivity [36,37]. Moreover, raised WBC has been identified as a feature of insulin resistance–related risk factor clustering independently of cigarette smoking [28]. There appear to be no previously published studies of relationships between insulin sensitivity and serum globulin concentrations or ESR, although a recent report noted a significantly higher ESR in those with insulin resistance–related risk factor clustering [28]. Our analysis excluded those with known cardiovascular disease or diabetes and those taking drugs for conditions that can be associated with subclinical inflammation. Therefore, there may have been relatively little subclinical inflammation in our study group. Had we evaluated C-reactive protein (CRP), closer associations might have been found, although studies conflict as to whether WBC or CRP is the stronger correlate of insulin sensitivity [11,37,38].

Comparatively strong correlations have been reported between hematocrit, hemoglobin, blood viscosity, and insulin sensitivity measured with the euglycemic hyperinsulinemic clamp or the insulin suppression test [12,39-41], but not with fasting plasma insulin and insulin resistance measured by homeostasis model assessment [42,43]. Our findings accord with those studies reporting relatively weak relationships between insulin sensitivity, hemoglobin, and hematocrit.

One other study, the Insulin Resistance Atherosclerosis Study, explored risk factor co-associations using factor analysis and the minimal model–derived measure of insulin sensitivity in a large group of individuals free of diabetes [44]. Uric acid concentration and GGT activity were not included in this analysis, and SBP and DBP were entered as separate variables into the factor analysis. Our analysis confirms a consistent finding in our previous analyses, namely, that only a single risk factor cluster centered on low insulin sensitivity can be distinguished. This contrasts with some, but not all [45], studies that have used factor analysis to assess insulin resistance–related co-associations. Further studies will be needed to establish whether the co-associations we observed are equally present in groups of comparable size and depth of investigation, but distinguished by sex, ethnicity, and socioeconomic status.

Our findings strongly support the inclusion of GGT activity and uric acid in studies of insulin resistance–related risk factor clustering. Our analysis also breaks new ground by suggesting that some correlates of low insulin sensitivity, in particular blood pressure and indices of subclinical inflammation, may not co-associate in a risk factor cluster, at least in the apparently healthy individuals in whom novel approaches to evaluation of disease risk are most warranted. This will need to be confirmed with other inflammation indices, particularly CRP, but does establish the principle that a risk factor may behave with respect to its co-associations with other risk factors very differently from its correlations.

Acknowledgment

The late Prof Victor Wynn initiated and established the HDDRISC study. We also thank the many clinical, scientific, technical, nursing, and administrative staff who have contributed to the study over the years, in particular, Drs Anthony Proudler, Carl Felton, Christopher Walton, David Crook, Raymond Bruce, Francisco Leya, and John Stevenson. This work was funded by the Atherosclerosis Research Trust, the Heart Disease and Diabetes Research Trust, and the Cecil Rosen Foundation.

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