Insulin resistance syndrome in postmenopausal women with cardiometabolic syndrome X

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Abstract

Objective—To determine whether postmenopausal women with cardiometabolic syndrome X (chest pain and abnormal exercise electrocardiogram despite normal coronary angiography) exhibit disturbances in the full range of proposed components of the putative “insulin resistance syndrome”.

Patients and methods—20 postmenopausal women with syndrome X and 20 healthy controls each underwent measurement of insulin resistance (by minimal model analysis of the intravenous glucose tolerance test), lipid, lipoprotein, and apolipoprotein concentrations, a range of haemostatic variables, serum uric acid concentration, and centrality of body fat distribution (by dual energy x ray absorptiometry).

Results—Women with syndrome X had higher fasting triglyceride concentrations than controls (median: 1.60 v 1.02 mmol/l, $P < 0.05$). Concentrations of high density lipoprotein cholesterol were lower (1.33 v 1.61 mmol/l, $P < 0.05$) as were those of the high density lipoprotein apolipoproteins AI and AII. Insulin and C peptide responses to the intravenous glucose tolerance test were higher (27.6 v 19.8 $\mu\text{U/ml/min}$, $P < 0.01$; 101 v 72 pmol/ml/min, $P < 0.05$, respectively), and insulin sensitivity was lower (1.89 v 3.09 min/ $\mu\text{U/ml}$, $P < 0.05$). There were, however, no significant differences between other proposed components of the insulin resistance syndrome (blood pressure, glucose tolerance, proportion of central body fat, serum uric acid concentration, and plasminogen activator inhibitor-1 activity). Antithrombin III activity was higher in women with syndrome X (121 v 113%, $P < 0.01$).

Conclusions—Women with syndrome X tend to be insulin resistant and have lipid and lipoprotein abnormalities, but do not exhibit all characteristics of the insulin resistance syndrome. Such variation in correlated risk factors is consistent with underlying heterogeneity in the insulin resistance syndrome and cardiometabolic syndrome X.

The term “syndrome X” was introduced in 1973 by Kemp¹ to acknowledge uncertainties over the aetiology of angina-like chest pain accompanied by angiographically normal coronary arteries. Conventional diagnostic criteria also include some further evidence of myocardial ischaemia, such as increased myocardial lactate production, reduced coronary sinus oxygen saturation, ST depression on exercise electrocardiogram, and impaired vasodilator reserve.² Inconsistencies in the expression of these features, however, indicate a degree of heterogeneity in the condition.³

There is increasing evidence that cardiometabolic syndrome X is accompanied by disturbances in metabolic risk factors for vascular disease, notably insulin resistance.^{4,5} Patients with syndrome X might therefore exhibit the putative “insulin resistance syndrome” (itself referred to as syndrome X or metabolic syndrome X).⁶ This syndrome has been invoked to account for reports of clustering among increased concentrations of insulin, glucose, and triglyceride, reduced concentrations of high density lipoprotein (HDL), and raised blood pressure.⁷ Experimental studies have provided evidence for biochemical and physiological links between insulin resistance and other risk factors for cardiovascular disease, thus supporting the hypothesis that insulin resistance is the abnormality that underlies this syndrome of metabolic disturbance.^{8,9}

We have previously demonstrated these disturbances in men with syndrome X,¹⁰ but other studies have suggested less consistent metabolic characteristics.^{4,5} There is also uncertainty over the importance of impaired glucose tolerance as a component of the insulin resistance syndrome, and controversy over the extent to which changes in blood pressure are directly related to disturbances in insulin metabolism.¹¹ Furthermore, new candidates for inclusion in the insulin resistance syndrome have been proposed, including increased concentrations of uric acid and increased activity of plasminogen activator inhibitor-1 (PAI-1).⁶ A central or android pattern of fat distribution may also be important.¹² These variables have yet to be explored in detail in patients with cardiometabolic syndrome X, as have intercorrelations between candidate components of the insulin resistance syndrome. In particular, there is a lack of metabolic information concerning syndrome X in women. Women comprise the majority of sufferers from the condition¹³ and an involvement of the menopause is suggested by their relatively high mean age.¹⁴

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In the present study, we undertook to determine whether insulin resistance syndrome was present in 20 postmenopausal women with syndrome X by comparing them with an age and weight matched group of healthy controls.

Patients and methods

PATIENTS

Women with syndrome X were recruited from a trial of transdermal oestrogen treatment. Inclusion in this trial required a history of anginal chest pain, a treadmill or bicycle exercise test with >1 mm ST depression in any lead, and a coronary angiogram considered normal—that is, not showing more than 30% stenosis, by two experienced observers. Left ventricular hypertrophy, mitral valve defect, or any other structural abnormality as diagnosed by chest radiograph or echocardiogram constituted exclusion criteria, as did any existing electrocardiogram (ECG) abnormalities likely to interfere with interpretation of an ECG during treadmill exercise testing, for example, left bundle branch block. Women with blood pressure greater than or equal to 160/100 mm Hg were also excluded. All recruits underwent evaluation for vasospastic angina (hyperventilation or ergonovine test) and all were negative. Four women had reversible perfusion defects on thallium scanning. Postmenopausal status (natural or surgical) was confirmed by amenorrhoea of at least 6 months duration, a follicle stimulating hormone level >40 IU/l, and an estradiol concentration <100 pmol/l. No hormone replacement treatment or cardiac medication (except glyceryl trinitrate as rescue medication) was allowed for 4 weeks before baseline studies. Of the 26 women who entered the trial, three were not white, two were grossly obese ($>145\%$ ideal body weight), and one had no insulin measurements during her intravenous glucose tolerance test (IVGTT). Studies carried out before treatment in the remaining 20 patients are evaluated in the present analysis.

Twenty healthy, non-hypertensive postmenopausal women attending a menopause clinic were selected to provide a control group of comparable age and weight to the patient group. Criteria for postmenopausal status were the same as for the women in the syndrome X group, but cigarette smokers were excluded. No drugs likely to affect carbohydrate or lipid metabolism were taken.

These studies were approved by the ethics committees of the Wynn Institute and the National Heart and Lung Institute and each participant gave written, informed consent.

PROCEDURES

All women were instructed to consume more than 200 g/day of carbohydrate for 3 days before their tests. Tests began between 0900 and 1000 after an overnight fast. Age, height, weight, time since menopause, and details of alcohol consumption, smoking, family history of diabetes and heart disease, and number of pregnancies were recorded. Exercise habit was

defined as 'aerobic' for those women who undertook, at least three times a week for 20 min or more, exercise requiring a noticeable increase in breathing rate, 'non-aerobic' for those who described themselves as taking only moderate exercise, and 'none' for those who described themselves as taking no exercise. Time since menopause for women who had undergone a hysterectomy was taken as the time since onset of menopausal symptoms. Numbers of close relatives (parents or siblings) with heart disease or diabetes were recorded. Blood pressure was measured after patients had rested in a semirecumbent position for 15 min. Indwelling cannulae were inserted into an antecubital vein in each arm, one for glucose administration and the other for sampling. Blood samples were taken for measurement of fasting plasma glucose, insulin, C peptide, serum lipid, and lipoprotein concentrations and factors of the coagulation and fibrinolytic systems. In two cases no samples were taken for coagulation and fibrinolytic assays due to technical problems. An additional sample was taken after 10 min for replicate measurement of fasting plasma glucose, insulin, and C peptide concentrations. An intravenous glucose injection (0.5 g glucose/kg body weight as a 50% (wt/vol) solution of dextrose) was given over 3 min and samples were taken at 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180 min. Regional distribution of fat and lean tissue was measured by dual energy x ray absorptiometry using a whole body scanner (DPX: Lunar Radiation, Madison, Wisconsin).

LABORATORY PROCEDURES

Plasma glucose was measured by a glucose oxidase technique.¹⁵ Plasma insulin and C peptide were measured using double antibody radioimmunoassays (Guildhay, Guildford, UK). Serum triglycerides, total cholesterol, and uric acid were measured using enzymatic methods. HDL cholesterol was measured after heparin manganese precipitation of other lipoproteins¹⁶ and HDL subfractions after further precipitation with dextran sulphate.¹⁷ Very low density lipoprotein (VLDL) cholesterol and triglyceride were measured after preparative ultracentrifugation at a solvent density of 1.006 g/l, and low density lipoprotein (LDL) cholesterol was estimated as the difference between total cholesterol and the sum of HDL and VLDL cholesterol. Apolipoproteins AI, AII, and B were measured by immunoturbidimetric assays,¹⁸ and Lp(a) lipoprotein by an enzyme linked immunosorbent assay (Biopool AB, Umea, Sweden). Plasma fibrinogen, factors VIIa and X, protein C and protein S were measured by nephelometric techniques on an automated coagulation analyser (ACL 100; Instrumentation Laboratory, Milan, Italy). Antithrombin III (AT III) and plasminogen were measured by enzymatic methods (Chromogenix, Mölndal, Sweden) on a discrete clinical analyser (Cobas Mira, Roche Diagnostics, Switzerland). Tissue plasminogen activator and PAI-1 were measured by

Table 1 Group characteristics in women with syndrome X and controls

	Women with syndrome X	Controls
n	20	20
Age (years)	58.0 (47–65)	57.0 (46–65)
Body mass index (kg/m ²)	26.3 (22.4–30.4)	25.6 (22.6–27.7)
Time since menopause (years)	7.5 (0–35)	6.5 (0–26)
No of patients who underwent hysterectomy (%)	40	15
Alcohol consumption (Units/week)	2.0 (0–21)	3.5 (0–21)
Cigarette smokers (%)		
Never	45	70
Previous	35	30
Current†	20	0
No of patients taking exercise (%)		
None	40	25
Non-aerobic	50	35
Aerobic†	10	40
Family history of diabetes mellitus (%)†	25	5
Family history of heart disease (%)	60	50
No of pregnancies (%)		
None	20	20
1–2	55	30
> 2	25	50

Values are median (range) unless otherwise specified. *The greater proportion of women with syndrome X who had a hysterectomy was of borderline significance ($P = 0.08$). †Proportions of current cigarette smokers and women with a family history of diabetes were significantly higher in the syndrome X group, and the proportion of women taking aerobic exercise significantly lower ($P < 0.05$) (Mann-Whitney U test).

manual enzymatic methods (Chromogenix) and fibrinopeptide A by radioimmunoassay (Byk-Sangtec, Dietzenbach, Germany).

DATA ANALYSIS

Android fat was estimated by dual energy x ray absorptiometry as the sum of fat mass in predefined waist and subscapular areas, and gynoid fat as the sum of hip and thigh fat.¹⁹ The ratio of fat in the android relative to the gynoid region was calculated, and proportions of android and gynoid fat were expressed as percentages of total body fat. Mean fasting plasma glucose, insulin and C peptide concentrations were derived from the two basal measurements. Incremental glucose, insulin, and C peptide areas (the area between the fasting level and the IVGTT concentration profile) were calculated by the trapezium rule. Insulin sensitivity (S_i) and glucose effectiveness were determined by minimal model analysis of the IVGTT glucose and insulin concentration profiles.²⁰ The relatively high glucose dose (0.5 g/kg) employed in the present studies allows for effective model identification,²¹ and insulin sensitivity estimates that

correlate well with those derived from the glycaemic clamp ($r = 0.92$).²² Insulin delivery characteristics were evaluated using the minimal model of post-hepatic insulin delivery, which provides measures of fractional insulin elimination rate (inversely related to the plasma insulin half-life), and measures of the responsiveness of first and second phase insulin delivery to glucose (ϕ_1 and ϕ_2 respectively). A combined model of insulin and C peptide delivery^{23,24} was used to quantify the fractional insulin elimination rate, a measure of the fraction of newly secreted insulin that passes out of the liver, and incremental pancreatic insulin secretion during the IVGTT. Models describing insulin delivery have been evaluated previously.^{21,23,25}

Differences between the groups were assessed by the Mann-Whitney U test. Relations between individual components of the insulin resistance syndrome were explored using Spearman's correlation. Statistical analyses employed BMDP statistical software (Los Angeles, California).

Results

The two groups did not differ significantly in age, body mass index, time since menopause or alcohol consumption, nor in the percentage of women with a family history of heart disease or in the number of pregnancies (table 1). Four women with syndrome X were current smokers compared with none in the control group. The percentages of women who had undergone hysterectomy and who had a family history of diabetes were higher in patients with syndrome X and the proportion of women who took aerobic exercise was lower.

There were no significant differences between women with syndrome X and controls in android to gynoid fat ratio (median: 0.91 *v* 0.90, respectively), percentage of android fat (32.0 *v* 32.6), percentage of gynoid fat (35.5 *v* 34.5), diastolic or systolic blood pressure (70 *v* 72 and 130 *v* 120 mm Hg), or serum uric acid concentrations (220 *v* 218 μ mol/l). Serum triglycerides were 57% higher in patients with syndrome X than in the controls and VLDL cholesterol and triglyceride were appropriately increased (table 2). HDL cholesterol was 17% lower, and apolipoprotein AI and apolipoprotein AII were 11% lower than in the control group. The lower HDL cholesterol levels were reflected in lower values for HDL₂ and HDL₃ cholesterol. Women with syndrome X had normal concentrations of total and LDL cholesterol, apolipoprotein B, and Lp(a) lipoprotein.

There were no differences between women with syndrome X and controls in fasting plasma concentrations of glucose (median: 5.29 *v* 5.10 mmol/l, respectively), insulin (0.065 *v* 0.065 pmol/ml) or C peptide (0.44 *v* 0.39 pmol/ml). Insulin and C peptide areas of the IVGTT were respectively 39% and 40% higher in patients with syndrome X than in controls and S_i was 39% lower (table 3). The

Table 2 Fasting serum lipid, lipoprotein and apolipoprotein concentrations in women with syndrome X and controls

	Women with syndrome X	Controls
n	20	20
Triglycerides (mmol/l)	1.60 (0.68–4.60)	1.02 (0.57–3.50)*
Total cholesterol (mmol/l)	5.99 (4.52–8.58)	5.76 (4.37–7.51)
LDL cholesterol (mmol/l)	4.35 (2.70–6.46)	3.76 (2.76–5.48)
HDL cholesterol (mmol/l)	1.33 (0.85–2.55)	1.61 (0.88–2.94)*
HDL ₂ cholesterol (mmol/l)	0.40 (0.07–1.40)	0.49 (0.10–1.69)
HDL ₃ cholesterol (mmol/l)	0.94 (0.68–1.25)	1.06 (0.78–1.33)
VLDL cholesterol (mmol/l)	0.43 (0.08–1.71)	0.20 (0.08–1.62)
VLDL triglyceride (mmol/l)	0.53 (0.17–3.24)	0.39 (0.15–2.23)
VLDL cholesterol/triglyceride molar ratio	0.52 (0.32–0.81)	0.57 (0.40–0.87)
Apolipoprotein AI (mg/dl)	132 (97–200)	149 (110–196)*
Apolipoprotein AII (mg/dl)	38 (29–52)	43 (36–55)*
Apolipoprotein B (mg/dl)	74 (48–108)	73 (43–98)
Lp(a) lipoprotein (mg/dl)	8.9 (0–85)	7.6 (0–55)

Values are median (range). * $P < 0.05$ *v* women with syndrome X (Mann-Whitney U test). LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein.

Table 3 Glucose, insulin, and C peptide responses to the intravenous glucose tolerance test (IVGTT) and model derived variables in women with syndrome X and controls

	Women with syndrome X	Controls
n	20	20
IVGTT incremental areas		
Glucose (mmol.l ⁻¹ .min)	528 (334–871)	550 (205–853)
Insulin (pmol.ml ⁻¹ .min)	27.6 (13.1–42.4)	19.8 (6.0–82.2)†
C peptide (pmol.ml ⁻¹ .min)	101 (50–190)	72 (35–201)*
Minimal model of glucose disappearance		
S _g (min ⁻¹)	1.70 (0.10–3.22)	1.46 (0.50–6.05)
S _i (min ⁻¹ .μU ⁻¹ .ml)	1.89 (0.06–9.15)	3.09 (0.68–7.91)*
Post-hepatic insulin delivery model		
n _i (min ⁻¹)	0.144 (0.040–0.257)	0.151 (0.022–0.240)
ϕ ₁ (μU.ml ⁻¹ .min.mg ⁻¹ .ml)	4.64 (1.28–13.78)	3.36 (1.99–21.14)
ϕ ₂ (μU.ml ⁻¹ .min ⁻² .mg ⁻¹ .ml)	10.9 (3.9–45.2)	9.2 (0.9–18.8)
Pancreatic insulin secretion model		
F	0.98 (0.42–2.19)	0.94 (0.54–1.69)
k _i (min ⁻¹)	0.080 (0.035–0.240)	0.110 (0.016–0.169)
IS _{inc} (pmol.ml ⁻¹ .min)	2.25 (1.36–4.84)	1.67 (0.21–6.45)

Values are median (range). *P < 0.05; †P < 0.01 (Mann-Whitney U test). S_g, glucose effectiveness; S_i, insulin sensitivity; n_i, fractional insulin elimination rate (post-hepatic insulin delivery model); ϕ₁, first phase insulin delivery to glucose; ϕ₂, second phase insulin delivery to glucose; F, fractional hepatic insulin throughput index; IS_{inc}, net increment in pancreatic insulin secretion during the IVGTT; k_i, fractional insulin elimination rate (pancreatic insulin secretion model).

Table 4 Factors of the coagulation and fibrinolytic systems in women with syndrome X and controls

	Women with syndrome X	Controls
n	18	20
Fibrinogen (mg/dl)	338 (236–417)	347 (222–518)
Factor VII (%)	120 (82–169)	126 (82–156)
Factor X (%)	119 (76–142)	112 (94–143)
Protein C (%)	124 (98–148)	124 (71–169)
Protein S (%)	118 (63–165)	104 (65–196)
Antithrombin III (%)	121 (103–130)	113 (97–134)*
Plasminogen (%)	108 (90–130)	114 (85–136)
Plasminogen activator inhibitor-1 (AU/ml)	8.2 (1.0–38.2)	5.2 (1.0–29.2)
Tissue plasminogen activator (IU/ml)	1.35 (0.20–4.80)	1.05 (0.30–2.60)
Fibrinopeptide A (ng/ml)	9.7 (3.7–79.6)	14.0 (3.1–89.0)

Values are median (range). *P < 0.01 (Mann-Whitney U test).

figure shows individual values for the S_i index. Despite the significant difference in S_i (P < 0.05) there was still appreciable overlap between the two groups, and this was also apparent with the other metabolic variables that differed significantly (data not shown). One patient with syndrome X had unusually high S_i. Exclusion of this patient's results did not affect the significance of the difference. The higher second phase post-hepatic insulin responsiveness (ϕ₂) and incremental pancreatic insulin secretion of patients with syndrome X were of borderline significance (P = 0.08). Glucose responses during the IVGTT did not differ between the groups. AT III was 7% higher in women with syndrome X than in

Insulin sensitivity (S_i) in postmenopausal women with cardiometabolic syndrome X (●) (n = 20) and in age and weight matched healthy controls (○) (n = 20). The median value is indicated by the horizontal line in each plot.

controls (table 4), otherwise there were no significant differences between coagulation and fibrinolytic factors.

Repeating these comparisons in analyses in which current smokers (n = 4), women who had undergone hysterectomy (n = 11), or those with a family history of diabetes (n = 6) were excluded did not affect the significance of the differences seen. Exclusion of those taking aerobic exercise (n = 10) reduced some significance levels, but in each of these comparisons the magnitude of the difference between the groups remained the same. For example, median S_i was between 36 and 44% lower, triglycerides between 48 and 75% higher, and HDL cholesterol between 13 and 24% lower in the remaining women with syndrome X.

Correlations between potential components of the insulin resistance syndrome were examined in the syndrome X and control groups separately. The magnitude of the correlations in each group were generally similar (results not shown), therefore these relations were evaluated in the study group as a whole. There were significant associations among percentage of android fat, serum triglyceride and HDL cholesterol concentrations, and insulin response to the IVGTT (table 5). S_i also correlated significantly with triglycerides and HDL, although the association with proportion of android fat was of borderline significance (r = -0.29, P = 0.06). PAI-1 concentrations decreased with increasing S_i and HDL cholesterol concentration and rose with increasing percentage of android fat (r = 0.31, P = 0.05). The only significant correlate of serum uric acid concentration was PAI-1 activity. Systolic blood pressure correlated with IVGTT insulin response, but only with borderline significance (r = 0.32, P = 0.07). Otherwise there were no associations between blood pressure and components of the insulin resistance syndrome. Interrelationships between S_i and several other variables were examined. There was a negative association between S_i and time since menopause (r = 0.37, P < 0.05) while no such association was seen with chronological age (r = 0.15, P > 0.3). AT III levels correlated with insulin response to the IVGTT (r = 0.40, P < 0.01) and S_i (r = 0.31, P = 0.06) and decreasing S_i was associated with increasing activity of factor X. (r = -0.33, P < 0.05).

Table 5 Univariate correlation coefficients (Spearman) among components of the insulin resistance syndrome for women with syndrome X and controls (n = 40)

	Android fat (%)	Triglycerides	HDL	Insulin response to the IVGTT	Insulin sensitivity	Plasminogen activator inhibitor-1	Uric acid
Triglycerides	0.43†						
HDL cholesterol	-0.33*	0.64‡					
Insulin response to the IVGTT	0.36*	0.38*	-0.31*				
Insulin sensitivity	-0.29	-0.41†	0.38*	-0.55‡			
Plasminogen activator inhibitor-1	0.31	0.18	0.32*	0.24	-0.34*		
Uric acid	0.10	-0.17	0.05	0.16	-0.06	0.38*	
Systolic blood pressure	-0.00	0.14	0.00	0.32	-0.00	0.28	0.03

*P < 0.05; †P < 0.01; ‡P < 0.001 (Spearman test). HDL, high density lipoprotein; IVGTT, intravenous glucose tolerance test.

Discussion

This study shows that postmenopausal women with syndrome X tend to have insulin resistance, hyperinsulinaemia, increased triglyceride concentrations, and reduced HDL cholesterol concentrations compared with those of healthy postmenopausal women. The two groups were of comparable age and body mass index, although there were differences in other characteristics. An increased incidence of hysterectomy has previously been found in women with syndrome X¹⁴ and the fewer women taking aerobic exercise is to be expected. Cigarette smoking was an exclusion criterion for the studies from which the control group was drawn, so no inferences can be made regarding the difference in smoking habit between the two groups. The difference in family history of diabetes is unexpected and may be worth examining in larger samples. Nevertheless, in subgroup analyses it was apparent that the metabolic differences between the groups were present regardless of these differences in group characteristics.

While three of the characteristics of the insulin resistance syndrome, insulin resistance, high triglycerides, and low HDL cholesterol, were present in the cardiometabolic syndrome X group, blood pressure, glucose tolerance, PAI-1 activity, uric acid concentration, and body fat distribution did not differ from those of healthy controls. We have previously observed similarly reduced S_{L} , increased triglycerides, and reduced HDL cholesterol in men with syndrome X, but in that study the patients had significantly higher systolic blood pressure.¹⁰ Other studies have examined mixed groups of men and women. Where measured, S_{L} in those with syndrome X was also about 40% lower than in healthy controls.^{5,26} Glucose tolerance test studies have, with one exception,²⁷ been consistent with this finding.^{4,28} Most studies show increased triglycerides and reduced HDL cholesterol, although these differences are generally less profound than the differences in insulin related variables. Where reported, most studies also show little difference in body fat distribution or blood pressure. Small numbers in some of the studies described might underlie the inconsistent differences in lipid and lipoprotein concentrations reported, but the consistent lack of a difference in blood pressure suggests that insulin resistance and raised blood pressure may not be linked in this condition.

Intercorrelations between components of the insulin resistance syndrome have not been explored in previous studies of cardiometabolic syndrome X. We found significant associations between insulin resistance, increased triglycerides, reduced HDL cholesterol, and proportion of android fat. The inclusion of android fat in this cluster is noteworthy as women with syndrome X did not have an increased proportion of android fat, suggesting that while android fat is an important correlate of metabolic disturbance it is not a factor in the differences seen between healthy postmenopausal women and those with syn-

drome X. Increased PAI-1 activity was associated with low HDL cholesterol, low S_{L} and an increased proportion of android fat, as would be expected for a component of the insulin resistance syndrome. There were no associations, however, between PAI-1 and triglycerides or the insulin response to the IVGTT. PAI-1 activity was higher in women with syndrome X, but this was not statistically significant: possibly larger group sizes would have rendered this difference significant. Other factors of the coagulation and fibrinolytic systems have not previously been reported in women with syndrome X. The importance of the raised AT III activities in women with syndrome X is difficult to assess: there seems to be a biphasic association between AT III activities and vascular disease, low and high activities being associated with increased risk,²⁹ but there are no reports of increased thrombotic tendency in patients with cardiometabolic syndrome X. The positive associations among AT III, insulin resistance, and increased insulin levels suggest that increased AT III activities might be a candidate for the insulin resistance syndrome. Despite finding no significant differences in the activity of factor X between patients with syndrome X and controls, we found a positive association between S_{L} and factor X activity. We are not aware of any previous reports linking insulin resistance with increased AT III or factor X activities.

A heterogeneous manifestation of disturbances therefore seems to be associated with the insulin resistance syndrome among the women who we studied, with a core of correlations among S_{L} , triglycerides, and HDL cholesterol, probable involvement of android fat levels and PAI-1 activities, and no involvement of uric acid or blood pressure. Whether these differences and associations are sufficient for us to conclude that women with cardiometabolic syndrome X manifest the insulin resistance syndrome is arguable. This uncertainty is emphasised by the considerable overlap in individual values between the groups, even in those components of the insulin resistance syndrome that differed significantly. A serious shortcoming in many discussions of the insulin resistance syndrome has been a lack of diagnostic criteria: while correlations and differences in median values may be highly suggestive with regard to groups as a whole, they are insufficient to confer a diagnosis on an individual. Differentials between insulin resistance as it relates to the glucoregulatory, antilipolytic, and haemodynamic effects of insulin may yet undermine the central position ascribed to insulin resistance in the aetiology of correlated metabolic disturbances. Furthermore, it is becoming increasingly apparent that insulin resistance can itself be induced by many of the disturbances that are typical of the syndrome, making it difficult to justify a strict causal chain from insulin resistance to its various manifestations.⁹

In general, the prognosis of patients with cardiometabolic syndrome X is good,^{3,14} calling into question a role for insulin resistance in

the aetiology of coronary artery disease. Follow up studies of patients with syndrome X may have included a substantial proportion who were not insulin resistant. Alternatively, the long-term effects of insulin resistance associated with vascular dysfunction may differ from those of insulin resistance associated with more general, atherogenic metabolic derangement; moreover, a certain minimum complement of metabolic disturbances associated with insulin resistance may be needed to influence long-term health. To resolve these issues, future studies will need to pay particular attention to potential heterogeneity in the insulin resistance syndrome and cardiometabolic syndrome X.

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