European Journal of Clinical Nutrition (2006) 60, 802–809
 0954-3007/06 $30.00
www.nature.com/ejcn

ORIGINAL ARTICLE

Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin

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Background: Patients with metabolic syndrome (MS) have above-average risk of developing atherosclerosis and cardiovascular disease. Inflammation plays a key role in the development of atherosclerosis. High levels of the acute phase reactants C-reactive protein (CRP) and ferritin have been reported to correlate with various components of MS.
Patients and methods: The serum CRP, ferritin, glucose, insulin, triglycerides, HDL-cholesterol and total cholesterol concentrations of 598 obese or overweight patients were determined, together with relevant anthropometric parameters. Insulin resistance was evaluated by the HOMA method. MS was diagnosed using the ATP III criteria.
Results: CRP levels were higher among patients with central obesity than in those without (5.8 vs 3.9 mg/l; $P=0.003$), and higher among those with fasting plasma glucose concentrations $\geqslant$110 mg/dl than in those with lower concentrations (7.4 vs 4.1 mg/l; $P=0.01$). Serum ferritin levels were higher among patients with triglyceride concentrations $\geqslant$150 mg/dl than in those with lower levels (76.8 vs 40.1 ng/ml; $P<0.001$), and higher among those with fasting plasma glucose concentrations $\geqslant$110 mg/dl than in those with lower concentrations (75.7 vs 41.7 ng/ml; $P=0.005$). The number of MS criteria that were satisfied increased with CRP and ferritin levels. Patients with insulin resistance also had higher CRP and ferritin levels than those without, 7.3 vs 4.3 mg/l for CRP ($P=0.032$) and 124.5 vs 80.1 ng/ml for ferritin ($P<0.001$).
Conclusions: MS and insulin resistance are associated with elevated serum CRP and ferritin. Evaluation of subclinical chronic inflammation in patients with MS and/or insulin resistance by determination of these markers might aid in their evaluation as candidates for aggressive intervention against cardiovascular risk factors.
European Journal of Clinical Nutrition (2006) **60,** 802–809. doi:10.1038/sj.ejcn.1602384; published online 22 February 2006

Keywords: metabolic syndrome; inflammation; C-reactive protein; ferritin

Introduction

Inflammation is involved in insulin resistance, adiposity and other aspects of metabolic syndrome (MS). The evidence for this includes observations of association between high levels of the acute phase reactant C-reactive protein (CRP), a sensitive marker of subclinical inflammation, and insulin resistance or MS components (Frohlich *et al*., 2000a,b; Han *et al*., 2002; Ford, 2003; Sattar *et al*., 2003). High CRP is likewise predictive of diabetes (Pradhan *et al*., 2001; Thorand *et al*., 2003). Ferritin, another acute phase reactant, has also been related to insulin resistance (Fernandez-Real *et al*., 1998; Sheu *et al*., 2003), MS (Jehn *et al*., 2004) and diabetes (Jiang *et al*., 2004). However, now there is increasing evidence that elevated body iron stores, evaluated by serum ferritin, may be associated with hypertension, dyslipidaemia, elevated fasting insulin and blood glucose and central obesity.

Inflammation also plays a key role in the development of atherosclerosis, high CRP levels being predictive of cardiovascular disease (Kuller *et al*., 1996; Ridker *et al*., 1997, 2000). In keeping with this, MS patients have above-average risk of atherosclerosis and of atherosclerotic cardiovascular disease (Trevisan *et al*., 1998; Isomaa *et al*., 2001).

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Received 6 June 2005; revised 3 November 2005; accepted 11 November 2005; published online 22 February 2006

This study is approached with the idea of determining the association between basal CRP and ferritin levels and each of the components of the MS, as defined by the third report of the U.S. National Heart, Lung and Blood Institute's Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) (U.S. National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). In this study, we investigated the relationships between these markers of inflammation and MS and insulin resistance in a Spanish population.

Patients and methods

The initial candidates for inclusion in the study were the 634 consenting patients aged >18 years (218 men, 416 women) who, between January 1996 and December 2003, were treated in the Endocrinology and Nutrition Service of the Juan Canalejo Hospital (A Coruña, Spain) following diagnosis of obesity or excess weight in accordance with the criteria of the Spanish Society for the Study of Obesity (SEEDO) (Sociedad Española para el Estudio de la Obesidad (SEEDO), 2000). Of these 634, 36 were excluded because of the following exclusion criteria: neurological, endocrinological or other major systemic disease, including malignancy ($n=3$); a history or current clinical evidence of haemochromatosis (serum iron >190 μg/dl (men) or >175 μg/dl (women), serum ferritin >300 μg/l (men) or >200 μg/l (women), or transferrin saturation >60%) ($n=1$); history of drugs or alcohol abuse, defined as alcohol intake >80 g/day in men and >40 g/day in women, or serum transaminase activity more than twice the upper limit of the normal range ($n=6$); high serum creatinine concentration ($n=2$); occurrence of an acute major cardiovascular event in the previous 6 months ($n=3$); acute illness or current evidence of acute or chronic inflammatory or infective disease ($n=8$); treatment for anaemia within the past 3 months ($n=9$); cirrhosis or chronic hepatitis ($n=4$). The actual study group thus comprised 598 patients (203 men, 395 women). It included patients being treated for hypertension, dyslipidaemia or diabetes, whose therapeutic regimens were noted.

All patients included in the study were characterized anthropometrically by determining their weight (with a Seca balance), height (with a Holtain stadiometer), body mass index (BMI), and waist circumference accordance with the 1996 SEEDO definitions and procedures (Sociedad Española para el Estudio de la Obesidad, 1996).

Plasma glucose was determined enzymatically (Ter *et al*., 1984), and insulin by a radioimmunoassay (Berson and Yellow, 1959). Triglyceride, high-density lipoprotein (HDL) cholesterol and total cholesterol concentrations were measured by enzymatic assays using a Technicon RA1000 analyser (Ter *et al*., 1984). High-sensitivity CPR was analyzed by latex-enchanced nephelometry. Five categories were considered in the CRP levels (<0.5, 0.5 to <1, 1 to <3.3 to 10 and $\geqslant$10 mg/l), as was described in the women's health study (WHS) (Ridker *et al*., 2003), taking into account both extreme values (<0.5 and >10 mg/l), since their value was shown to be a protection and a risk value, respectively. Fasting ferritin was determined by means of an immunoradiometric assay (Bio-Rad, Hercules, CA, USA) and patients were classified accordingly into three ferritin intervals: <30, (30–74.9) and $\geqslant$75 ng/ml.

Blood pressure (BP) was measured in duplicate using a standard sphygmomanometer with the patient supine, after 10 and 15 min in this position. In accordance with the recommendations of the ATP III (U.S. National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001), patients with BP $\geqslant$130/85 mmHg were considered as hypertensive. Patients being treated for hypertension who were normotensive at the time of the study were also considered as hypertensive subjects.

Insulin resistance was defined in terms of the Homeostasis Model Assessment (HOMA) score (Matthews *et al*., 1985), $HOMA_{IR}$ = [fasting insulin (μU/ml) $\times$ fasting glucose (mmol/l)]/22.5 as being indicated by a $HOMA_{IR}$ score greater than the third quartile of the $HOMA_{IR}$ distribution of the non-diabetic population, which was determined, using the non-diabetic patients of the present study as a sample, as 3.99 (Gupta *et al*., 2003).

Metabolic syndrome was diagnosed in accordance with ATP III criteria (U.S. National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001) if three or more of the following conditions were observed:

(1) Central obesity: waist circumference >102 cm for men or >88 cm for women.
(2) Hypertriglyceridaemia: serum triglycerides $\geqslant$150 mg/dl (1.7 mmol/l).
(3) Low HDL cholesterol <40 mg/dl (1.1 mmol/l) for men or <50 mg/dl (1.3 mmol/l) for women.
(4) Arterial hypertension: $\geqslant$130/85 mmHg or antihypertensive treatment.
(5) Hyperglycaemia: fasting plasma glucose $\geqslant$110 mg/dl.

Statistical analyses

The statistical distributions of continuous variables were checked for normality using the Kolmogorov–Smirnov test, and the statistical significance of differences between groups was evaluated using Student's *t*-test or the Mann–Whitney test, as appropriate. Between-group differences in percentage data were assessed using the χ^2-test. Correlation between continuous variables was evaluated in terms of Spearman's ρ. Multiple linear regression was used to identify MS components with independent value as predictors of CRP or ferritin following logarithmic transformation of the latter variables. The ability of CRP and ferritin to discriminate between patients who satisfied the criteria for MS or insulin resistance and patients who did not was evaluated in terms of the areas

under ROC curves. All tests were two-sided, and the criterion for statistical significance was in all cases $P<0.05$. All statistical analyses were performed using SPSS 12.0 for Windows.

Results

Mean patient age was 38.4 years (s.d. 16.0 years). On average, male patients were significantly younger than female patients (mean 33.5 vs 41.0 years; $P<0.001$), and had significantly lower HDL cholesterol levels (mean 40.5 vs 48.4 mg/dl; $P<0.001$), larger waist circumferences (mean 105.8 vs 91.6 cm; $P<0.001$), and higher triglyceride levels (mean 154.9 vs 111.9 mg/dl; $P<0.001$). However, the sexes did not differ significantly as regards BMI (mean for the whole study group 32.4 kg/m^2, s.d. 5.4 kg/m^2, median 31.6 kg/m^2), blood pressures, or fasting glucose (see Table 1 for whole-group descriptive statistics). Among men the prevalence of both MS (32.7%) and insulin resistance (35%) were greater than among women (25.5 and 26.7%, respectively), although in neither case was the difference statistically significant. Men and women did not differ significantly as regards CRP levels (mean among men 4.0 mg/l, mean among women 5.1 mg/l, $P=0.233$), but men had significantly higher ferritin levels (171.4 vs 54.0 ng/ml; $P<0.001$).

Mean serum CRP concentration in the whole study group was 4.7 mg/l; median, 3.2 mg/l; and range, 15–35.0 mg/l. On average, patients who satisfied the overall ATP III criterion for MS had higher CRP levels than those who did not (mean 7.2, median 5 mg/l vs mean 3.6, median 3 mg/l), and CRP levels tended to increase with the number of individual MS criteria that were satisfied (Table 2). Of the five component ATP III criteria of MS, two (waist circumference and glucose) were satisfied by increasing percentages of patients in successively higher CRP strata, and the other three were also satisfied by greater percentages of patients in the top two strata (CRP $\geqslant$3 mg/l) than in the lower strata (Table 3). CRP levels were also significantly higher among patients satisfying the ATP III waist circumference and serum glucose criteria than among those who did not, with means of 5.8 vs 3.9 mg/l ($P=0.003$) in the case of the waist circumference criterion and 7.4 vs 4.1 mg/l ($P=0.01$) for the glucose criterion, whereas there was no such difference for any of

Table 2 CRP and ferritin levels in classes defined by the number of individual MS criteria satisfied

No. of ATPIII MS criteria	*CRP (mg/l)*		*Ferritin (ng/ml)*	
	Mean (s.d.)	*Median*	*Mean (s.d.)*	*Median*
0	4.3 (6.6)	2	54.0 (46.8)	39.7
1	4.5 (4.1)	3.1	64.4 (67.2)	39.7
2	4.1 (3.2)	3.3	80.0 (90.1)	54.0
$\geqslant$3	7.2 (7.0)	5.0	128.4 (138.8)	69.5

s.d., standard deviation; MS, metabolic syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; ATP III, Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

Table 1 Anthropometric and biochemical features of the overweight or obese subjects included in the study

	Totals		
	Mean (s.d.)	*Median*	*Range*
Systolic blood pressure (mmHg)	126.2 (12.9)	120.0	100.0–190.0
Diastolic blood pressure (mmHg)	74.2 (7.5)	70.0	60.0–100.0
Waist circumference (cm)	96.6 (14.1)	97.0	68.0–147.0
HDL (mg/dl)	46.0 (11.3)	44.0	22.0–85.0
Triglycerides (mg/dl)	124.3 (78.6)	103.5	25.0–814.0
Fasting glucose (mg/dl)	101.2 (24.0)	96.0	46.0–321.0
Fasting insulin (μU/ml)	13.3 (8.3)	11.8	1.5–107.6
CRP (mg/l)	4.7(5.3)	3.2	15.0–35.0
Ferritin (ng/ml)	84.0 (98.9)	46.3	6.2–563.1
Satisfaction of ATP III MS criteria		in %	
Waist circumference ($>$102 cm in males and $>$88 cm in females)		56.8	
Triglycerides ($\geqslant$150 mg/dl)		24.1	
Glucose ($\geqslant$110 mg/dl)		18.9	
HDL ($<$ 40 mg/dl in males and $<$ 50 mg/dl in females)		55.4	
Hypertension ($\geqslant$130/85 mmHg or treatment)		38.7	
ATP III MS		27.0	
Other MS criterion		in %	
Insulin resistance (HOMA$>$percentile 75)		29.1	

s.d., standard deviation; MS, metabolic syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; HOMA, Homeostasis Model Assessment; ATP III, Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

Table 3 Percentages of patients in each of five CRP classes satisfying or not satisfying the overall ATP III criterion of MS and the individual component criteria, with descriptive statistics of each category in each case

	CRP(mg/l)							
	<0.5	*0.5–1*	*1–3*	*3–10*	*⩾10*	*Mean (s.d.)*	*Median*	P
ATPIII MS								
Yes	0%	14.3%	9.5%	30.2%	40.0%	7.2 (6.9)	5.0	0.003
No	100%	85.7%	90.5%	69.8%	60.0%	3.6 (3.3)	3.0	
Waist perimeter								
>102 cm in males and >88 cm in females	0%	13.3%	48.4%	52.0%	60.0%	5.8 (5.5)	4.0	0.003
⩽102 cm in males and ⩽88 cm in females	100%	86.7%	51.6%	48.0%	40.0%	3.9 (5.1)	2.6	
Triglycerides								
⩾150 mg/dl	0.0%	28.6%	16.7%	40.0%	38.5%	5.4 (5.2)	4.0	0.081
<150 mg/dl	100.0%	71.4%	83.3%	60.0%	61.5%	4.2 (4.5)	3.0	
HDL								
<40 mg/dl in males and <50 mg/dl in females	0%	53.8%	26.1%	46.7%	30.8%	4.6 (4.4)	3.8	0.701
⩾40 mg/dl in males and ⩾50 mg/dl in females	100%	46.2%	73.9%	53.3%	69.2%	4.6 (5.0)	3.0	
Hypertension								
⩾130/85 mmHg or treatment	25.0%	14.3%	26.9%	34.1%	30.8%	5.8 (6.5)	4.0	0.078
<130/85 mmHg without treatment	75.0%	85.7%	85.7%	65.9%	69.2%	4.1 (5.0)	3.0	
Glucose								
⩾110 mg/dl	0%	0%	8.3%	20.0%	23.1%	7.4 (6.9)	5.2	0.010
<110 mg/dl	100%	100%	91.7%	80.0%	76.9%	4.1 (4.1)	3.0	

s.d., standard deviation; MS, metabolic syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; ATP III, Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

Table 4 Spearman's ρ values for correlation between CRP or ferritin and clinical or biochemical parameters

	C-reactive protein (mg/l)		*Ferritin (ng/ml)*	
	ρ	P	ρ	P
Waist circumference	0.203	0.029	0.368	<0.001
Systolic blood pressure	0.256	0.011	0.098	0.289
Diastolic blood pressure	0.236	0.019	0.149	0.107
HDL	−0.013	0.902	−0.143	0.057
Triglycerides	0.222	0.027	0.263	<0.001
Glucose	0.124	0.220	0.316	<0.001
HOMA	0.270	0.011	0.291	<0.001

s.d., standard deviation; MS, metabolic syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; HOMA, Homeostasis Model Assessment; ATP III, Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

the other three criteria (the high-triglycerides and high-BP groups did have higher CRP levels than the corresponding low-value groups, but these differences were not statistically significant). Surprisingly, when MS component values in the whole study group were considered it was not only HDL cholesterol for which there was no statistically significant correlation with CRP, but also fasting glucose (Table 4). However, multiple regression analysis showed the only MS criteria, satisfaction of which had independent value for prediction of CRP, to be those concerning waist circumference ($\rho = 0.630$, $P = 0.011$) and glucose ($\rho = 0.936$, $P = 0.035$).

Mean serum ferritin concentration in the whole study group was 84.0 ng/ml (median 46.3, and range 6.2–563.1 ng/ml). Like CRP, ferritin was on average higher among patients who satisfied the overall ATP III criterion of MS than among those who did not (mean 133.9 vs 66.8 ng/ml, median 70.4 vs 40.1 ng/ml), and ferritin levels tended to increase with the number of individual MS criteria that were satisfied (Table 2). The ATP III criteria concerning waist circumference, triglycerides and glucose were satisfied by increasing percentages of patients in successively higher ferritin strata, but the reverse was true for the HDL-cholesterol criterion and there was no coherent trend in the hypertension data (Table 5). Ferritin levels were also significantly higher among patients satisfying the ATP III triglycerides and serum glucose criteria than among those who did not, with means of 128.0 vs 66.6 ($P < 0.001$) and 108.3 vs 80.3 ng/ml ($P = 0.005$), respectively, while the higher ferritin levels of those satisfying the waist circumference criterion (99.3 vs 71.4 ng/ml) were of borderline statistical significance ($P = 0.05$). In the whole study group, serum ferritin concentration was significantly correlated with waist circumference, triglycerides and glucose, but not with HDL cholesterol or blood pressures (Table 4). However, multiple regression analysis showed the MS components, satisfaction of which had independent value

Table 5 Percentages of patients in each of three ferritin classes satisfying or not the overall ATP III criterion of MS and the individual component criteria, with descriptive statistics of each category in each case

	Ferritin (ng/ml)					
	<30	*30–74.9*	*⩾75*	*Mean (s.d.)*	*Median*	P
ATPIII MS						
Yes	21.3%	26.9%	43.4%	133.9 (141.1)	70.4	
No	78.7%	73.1%	56.6%	66.8 (71.8)	40.1	0.002
Waist circumference						
>102 cm in males and >88 cm in females	47.3%	50.9%	65.0%	99.3 (112.4)	55.0	0.05
⩽102 cm in malesand ⩽88 cm in females	52.7%	49.1%	35.0%	71.4 (86.0)	39.3	
Triglycerides						
⩾150 mg/dl	21.1%	23.8%	47.5%	128.0 (131.1)	76.8	<0.001
<150 mg/dl	78.9%	76.2%	52.5%	66.6 (77.6)	40.1	
HDL						
<40 mg/dl in males and <50 mg/dl in females	61.1%	48.4%	47.5%	86.1 (108.4)	41.9	0.088
⩾40 mg/dl in males and ⩾50 mg/dl in females	38.9%	51.6%	52.5%	88.4 (94.7)	55.0	
Hypertension						
⩾130/85 mmHg or treatment	30.8%	27.5%	35.9%	103.8 (135.1)	47.2	0.474
<130/85 mmHg without treatment	69.2%	72.5%	64.1%	71.3 (78.9)	41.5	
Glucose						
⩾110 mg/dl	8.9%	20.6%	29.5%	108.3 (100.0)	75.65	0.005
<110 mg/dl	91.1%	79.4%	70.5%	80.3 (101.2)	41.7	

s.d., standard deviation; MS, metabolic syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; ATP III, Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

Table 6 Serum CRP and ferritin levels in patients with and without insulin resistance as defined by the HOMA method

	Insulin resistance[a]		
	Yes	*No*	P
CRP (mg/l)			
Mean (s.d.)	7.3 (4.7)	4.3 (4.7)	0.032
Median	6.35	3.0	
Range	0.8–15.0	0.18–29.0	
Ferritin (ng/ml)			
Mean (s.d.)	124.5 (112.0)	80.1 (100.6)	<0.001
Median	86.3	42.0	
Range	13–504.0	1.4–563.1	

[a]Defined as having HOMA (fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5) values above the 75th percentile of the distribution in the non-diabetic subgroup (⩾3.99).
s.d., standard deviation; MS, metabolic syndrome; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; HOMA, Homeostasis Model Assessment; ATP III, Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

for prediction of serum ferritin concentration, to be the triglycerides criterion ($\rho = 0.626$, $P = 0.013$), HOMA >percentile 75 ($\rho = 0{,}740$, $P = 0{,}035$) and, with borderline significance, the HDL criterion ($\rho = -0.456$, $P = 0.05$)

$HOMA_{IR}$ values were positively correlated with both CRP ($\rho = 0.270$, $P = 0.011$) and ferritin ($\rho = 0.291$, $P < 0.001$), with the result that patients satisfying the criterion for insulin resistance (see Patients and Methods) had significantly higher values of both these parameters than patients who did not, with means of 7.3 as against 4.3 mg/l for CRP ($P = 0.032$) and 124.5 vs 80.1 ng/ml for ferritin ($P < 0.001$) (Table 6).

Finally, the area under the ROCs for CRP as a marker of ATP III MS and insulin resistance was in both cases greater than the area under the corresponding ROC for ferritin, although the difference was in neither case statistically significant (Figures 1 and 2).

Discussion

For both CRP and ferritin, this study of patients for whom numerous sources of inflammation had been ruled out as a prerequisite for their inclusion in the study found significant positive relationships with insulin resistance, with several criteria of MS (particularly those concerning waist circumference, plasma glucose and serum triglycerides), and with the corresponding continuous criterion variables. In the case of CRP, these findings agree with those of several other studies in which high levels of this acute phase reactant – the concentration of which in serum is <3 mg/l in 90% of

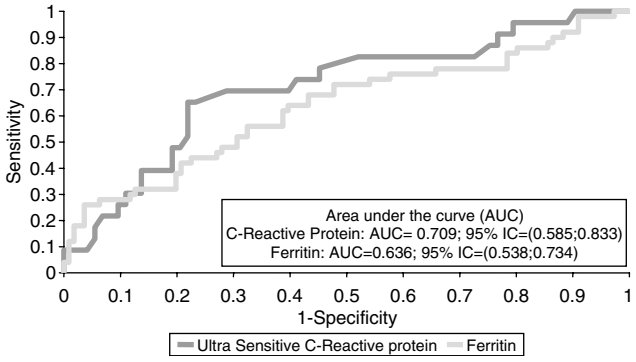

Figure 1 ROC curves for CRP and ferritin as markers of ATP III MS.

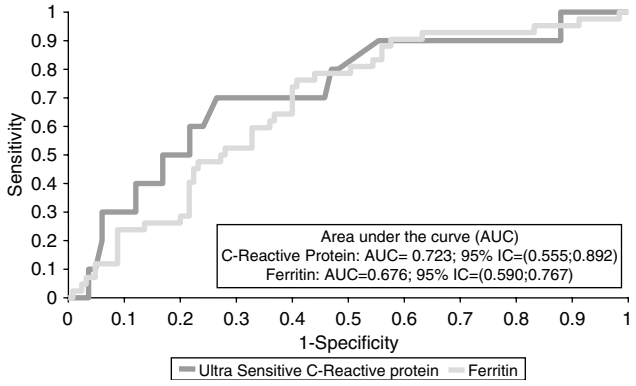

Figure 2 ROC curves for CRP and ferritin as markers of insulin resistance as defined on the basis of HOMA scores.

apparently healthy individuals (Pepys, 1996) – have been associated with insulin resistance, MS, MS components (hypertension, dyslipidaemia, etc.) or diabetes (Hak *et al*., 1999; Yudkin *et al*., 1999; Festa *et al*., 2000; Frohlich *et al*., 2000a, b; Pannacciulli *et al*., 2001; Gourdy *et al*., 2002; McLaughlin *et al*., 2002; Ford, 2003). The pathophysiological nature of these associations is unclear, but it has been reported that plasminogen activator inhibitor 1, another inflammatory marker of MS, insulin resistance and diabetes (Festa *et al*., 2002), is correlated with CRP (Festa *et al*., 2002) and is promoted by CRP in aortic endothelial cells (Devaraj *et al*., 2003), and it has been suggested that MS may be the result of a long-term hypersensitive reaction (Pickup and Crook, 1998). An alternative hypothesis is that it is insulin resistance that causes high CRP levels by reducing insulin-induced suppression of hepatic acute phase reactants (Campos and Baumann, 1992).

CRP is also high in atherosclerosis, and constitutes an independent marker of risk of future cardiovascular disease (Molina *et al*., 1990; Ridker *et al*., 1997, 2000, 2001; Yudkin *et al*., 1999; Pasceri *et al*., 2000; Gourdy *et al*., 2002). This implies that its measurement may assist the selection of preventive therapy for patients for whom intermediate risk of cardiovascular disease has been identified on other grounds (Pearson *et al*., 2003), and suggests that inflammation plays a key role in the development of atherothrombosis (Pickup and Crook, 1998). The mechanism of this action seems likely to involve CRP binding to the membranes of damaged cells, activating complement or enhancing the production of thrombogenic agents (Suankratay *et al*., 1998; Jarva *et al*., 1999; Yeh and Willerson, 2003), and the resulting vascular inflammation may contribute to the development of insulin resistance. A common inflammatory origin of both MS and atherosclerosis (Festa *et al*., 2002) would be in keeping with the above-normal prevalence of atherosclerotic disease among MS patients (Trevisan *et al*., 1998; Isomaa *et al*., 2001).

There is also increasing evidence of a relationship between MS, individual MS components, insulin resistance and type 2 diabetes on the one hand, and, on the other, high levels of iron deposits as measured by the concentration of the acute phase reactant ferritin in serum (Merkel *et al*., 1988; Dmochowski *et al*., 1993; Fernandez-Real *et al*., 1998; Salonen *et al*., 1998; Gillum, 2001; Piperno *et al*., 2002; Sheu *et al*., 2003; Jehn *et al*., 2004; Jiang *et al*., 2004), although the nature of this relationship is far from completely elucidated. For example, while elevation of ferritin levels seems clearly to precede the development of diabetes (Gillum, 2001; Jiang *et al*., 2004), the temporal relationship with MS is less clear (Jehn *et al*., 2004). However, it seems likely that increased ferritin reflects both the involvement of inflammation, as CRP does, and independent actions of excess iron. It is known that increased accumulation of iron affects insulin synthesis and secretion in the pancreas (Wilson *et al*., 2003) and interferes with the insulin-extracting capacity of the liver (Niederau *et al*., 1984), thereby leading to peripheral hyperinsulinaemia and impaired insulin secretion; that deposition of iron in muscle reduces glucose uptake because of muscle damage; (Merkel *et al*., 1988) and that iron accelerates atherosclerosis and damages endothelium in experimental models (Araujo *et al*., 1995; Lekakis *et al*., 1999) (catalytic iron converts relatively unreactive radical species such as H_2O_2 into highly reactive species such as hydroxyl radical, and thereby favours oxidative attack on cell membranes and other cell components) (Oberley, 1988; Wolff, 1993; Andrews, 1999; Beard, 2001). Since insulin in turn stimulates cellular iron uptake by increasing the externalization of transferrin receptor, and may also stimulate the production of erythropoietin (Davis *et al*., 1986), a vicious circle leading to insulin resistance and diabetes may set in. It has also been suggested that iron accumulation can be triggered by MS and/or genetic factors through the development of steatosis (Roetto *et al*., 2003; Den Boer *et al*., 2004; Robson *et al*., 2004), which might alter hepatic production of hepcidin, a protein that regulates central iron metabolism by modulating either intestinal absorption or macrophage recycling (Ganz, 2003). Although patients with several known causes of inflammation other than MS or insulin resistance were excluded from this study, other

possible influences on CRP or ferritin levels were not thus excluded or taken into account in the statistical analyses. They include burns, the recent use of aspirin and other nonsteroidal anti-inflammatory drugs, and recent magnesium intake, which affect CRP levels; (Hrebicek *et al*., 2002) and recent blood donation, which lowers iron reserves and increases sensitivity to insulin (Fernadez-Real *et al*., 2005). Also, CRP was measured in just a single blood sample; and insulin resistance was evaluated using the HOMA method on the basis of fasting glucose and insulin levels rather than by means of a euglycaemic-hyperinsulinaemic clamp. However, HOMA and clamp results are known to be highly correlated (Matthews *et al*., 1985; Merkel *et al*., 1988).

In conclusion, elevated serum CRP and ferritin levels show that patients with MS and/or insulin resistance tend to exhibit a certain degree of inflammation that, in one way or another, is likely to increase their risk of developing cardiovascular disease and/or diabetes. Determination of the serum CRP and ferritin concentrations of patients with MS and/or insulin resistance might thus aid their evaluation as candidates for aggressive intervention against cardiovascular risk factors.

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