

Prevalence of Body Iron Excess in the Metabolic Syndrome

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The metabolic syndrome, clinically defined by the Adult Treatment Panel III (ATPIII) (1), affects ~25% of western adults (2). The metabolic syndrome is closely linked to insulin resistance and implies an increased cardiovascular risk (3,4). Accumulating evidence suggests a link between body iron excess and insulin metabolism (5). Studies have shown an association between serum ferritin and one or more metabolic syndrome feature (6–11). Moreover, a syndrome characterized by hepatic iron overload (HIO) associated with insulin resistance features (insulin resistance-associated HIO [IR-HIO]), unrelated to genetic hemochromatosis, has been described (12,13). IR-HIO currently represents the most frequent indication to venesection in referral care units for iron overload (14). Data on the other side of the phenomenon, namely the prevalence of a potentially relevant iron overload in subjects selected for having metabolic syndrome, are scanty.

RESEARCH DESIGN AND METHODS

Within the registry of the Verona Heart Project (15), we identified metabolic syndrome subjects according to ATPIII because of three or more of the following: 1) fasting glucose ≥ 110 mg/dl or antidiabetes medication, 2) hy-

per-tension (blood pressure $\geq 135/85$ mmHg or medication), 3) triglycerides ≥ 150 mg/dl, 4) HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women, and 5) obesity (BMI ≥ 27 kg/m² instead of waist circumference, due to unavailability of waist circumference measurement in all subjects). An age-matched control group was extracted from the registry, requiring the absence of either metabolic syndrome or any evidence of cardiovascular disease. We excluded patients who were homozygous for the main HFE mutation associated with genetic hemochromatosis (C282Y) or who had any condition affecting the specificity of serum ferritin as an indicator of body iron stores: 1) recent acute illness and/or history of any overt chronic inflammatory disease; 2) cirrhosis, chronic hepatitis, and/or liver enzymes two or more times the upper normal limit (alanine aminotransferase 45 units/l, aspartate aminotransferase 40 units/l); 3) heavy drinkers (> 60 g alcohol/day); and 4) neoplastic disease. A total of 479 subjects (269 metabolic syndrome and 210 control subjects) were eligible. Laboratory analyses, including high-sensitivity C-reactive protein (hs-CRP), were performed as described (15,16). According to an international consensus (17,18), a potentially relevant iron overload was defined

as ferritin > 300 $\mu\text{g/l}$ in men and > 200 $\mu\text{g/l}$ in women.

RESULTS— Table 1 reports the characteristics of the study population. Mean ferritin levels were higher in metabolic syndrome subjects than in control subjects and increased linearly with the increasing number of metabolic syndrome features (mean values in $\mu\text{g/l}$ [95% CI]: 60.7 [49.1–76.5], 105.3 [94.3–117.5], and 142.3 [121.1–167] for none, one to three, and more than three metabolic syndrome features, respectively; $P < 0.001$ by ANOVA). None of the metabolic syndrome features (or C282Y heterozygosity) were significantly different between metabolic syndrome subjects with or without hyperferritinemia (not shown). The prevalence of iron overload was significantly higher in metabolic syndrome subjects than in control subjects (Table 1). Further genotyping of hyperferritinemic subjects for the HFE H63D mutation yielded 19 heterozygous (11 metabolic syndrome and 8 control subjects) but no H63D homozygous or C282Y/H63D compound heterozygous. All of the metabolic syndrome characteristics were significantly associated with ferritin (Spearman's coefficients: HDL: $\rho = -0.3$, $P < 0.001$; BMI: $\rho = 0.25$, $P < 0.001$; triglycerides: $\rho = 0.21$, $P < 0.001$; glucose: $\rho = 0.14$, $P = 0.003$; homeostasis model assessment: $\rho = 0.12$, $P = 0.01$; hs-CRP: $\rho = 0.15$, $P = 0.001$; insulin: $\rho = 0.09$, $P = 0.05$). Independent associations between body iron excess and metabolic syndrome features were tested by a series of multiple linear or logistic regression models using (log)ferritin or hyperferritinemia as the dependent variable, respectively. The best models indicated triglyceride-to-HDL cholesterol ratio, commonly considered a good indicator of defective insulin action (2), and BMI as independent predictors (linear model: $R^2 = 12.3\%$, standardized β coefficients = 0.24 [$P < 0.001$] for triglyceride-to-HDL cholesterol ratio and 0.162 [$P < 0.02$] for BMI; logistic model: odds ratio 3.49 [95% CI 1.28–9.52] for triglyceride-to-HDL cholesterol ratio [$P = 0.014$]). The addition of hs-CRP or ho-

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Abbreviations: ATPIII, Adult Treatment Panel III; HIO, hepatic iron overload; hs-CRP, high-sensitivity C-reactive protein; IR-HIO, insulin resistance-associated HIO.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical and biochemical data of metabolic syndrome and control subjects

	Metabolic syndrome subjects	Control subjects	P*
n	269	210	
Age (years)†	58.7 (57.5–59.9)	57.4 (55.6–59.2)	0.219
Male sex (%)	79.6	65.2	<0.001
BMI (kg/m ²)†	28.5 (28.1–28.9)	24.5 (24.0–24.9)	<0.001
Glucose (mmol/l)‡	6.30 (6.11–6.50)	5.31 (5.22–5.40)	<0.001
Triglycerides (mmol/l)‡	2.27 (2.15–2.39)	1.27 (1.21–1.34)	<0.001
LDL cholesterol (mmol/l)‡	3.70 (3.57–3.83)	3.45 (3.33–3.57)	0.007
HDL cholesterol (mmol/l)‡	1.02 (0.99–1.05)	1.48 (1.43–1.53)	<0.001
Hypertension (%)	73.3	22.0	<0.001
Insulin (μU/ml)‡	14.77 (13.81–15.80)	12.32 (11.44–13.28)	<0.001
HOMA‡§	4.14 (3.88–4.58)	2.92 (2.69–3.16)	<0.001
hs-CRP (mg/l)‡	2.97 (2.61–3.39)	1.65 (1.40–1.95)	<0.001
Ferritin (μg/l)‡	124.0 (111.2–138.2)	82.7 (72.6–94.3)	<0.001
C282Y heterozygotes (%)	3.7	6.5	0.178
Prevalence of body iron excess (%)	14.5	8.1	0.03

*Quantitative data were analyzed by Student's unpaired *t* test; qualitative variables by χ^2 . †Data are means (95% CI). ‡Skewed variables, for which data are geometric means (95% CI). §Homeostasis model assessment (HOMA) (30) was calculated as fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5. ||Odds ratio 1.92 (95% CI 1.05–3.5).

meostasis model assessment did not affect the results.

CONCLUSIONS— As described in 1997, IR-HIO drew attention to a clinical-pathological entity of primary HIO that was unlinked to genetic hemochromatosis (12,13). In that context, criteria for defining insulin resistance were generous compared with ATPIII standards (1): anyone with BMI >25 kg/m² was considered obese, and any hyperlipidemia (without considering the typical changes of insulin resistance/metabolic syndrome) was included. Nonetheless, the description of IR-HIO meritoriously disclosed a clinical entity at high risk of hepatic fibrosis (19), which probably lies at one end of the spectrum of insulin resistance–related iron overload (5). We explored the other end. The prevalence of biochemical iron overload within the wide metabolic syndrome population is presently unknown. We defined metabolic syndrome according to the ATPIII, with the sole exception of obesity. However, we used a BMI cutoff (27 kg/m²) well within the values (26.1–27.8 kg/m²) showing an association between obesity and insulin resistance (20,21) and commonly accepted in population studies (22). Measurement of serum ferritin is a reliable tool for estimating body iron stores in epidemiological studies, providing that confounding effects by inflammatory, hepatic, or neoplastic dis-

eases are excluded (23). Indeed, our major effort was to exclude any genetic/acquired confounding condition. Under the strict criteria adopted, we found that far less than one of six metabolic syndrome subjects has biochemical iron overload. Considering the prevalence of metabolic syndrome in the general population and that, at present, iron metabolism is not regularly investigated in metabolic syndrome, this could imply a relevant absolute number of subjects at risk for iron-related tissue damage. The mechanistic link between iron overload and metabolic syndrome remains unclear. Our models indicated obesity and dyslipidemia (triglyceride-to-HDL cholesterol ratio) among the metabolic syndrome features, with the strongest/independent association with iron overload. It is noteworthy that hs-CRP did not influence the results, suggesting that the known relationship between subclinical inflammation and metabolic syndrome (24) is unlikely to play a prominent role in determining serum ferritin in these patients. Since only a proportion of metabolic syndrome subjects (14.5%) appears at risk for iron overload, a “second hit” may be needed in susceptible individuals. Recently, hepcidin, a disulfide-rich peptide produced by hepatocytes, emerged as the central regulator of iron metabolism, modulating either intestinal absorption or macrophage

recycling (25). Altered hepcidin production as a result of metabolic syndrome–related steatosis (26) and/or concomitant genetic predisposition (27,28) may be an attractive explanation and is awaiting further exploration. Similarly, more accurate measurement of iron stores by invasive (liver biopsy) and/or expensive techniques (magnetic resonance) (29), both unfeasible in population studies, are needed to clarify the prevalence of overt IR-HIO in metabolic syndrome patients with biochemical iron overload.

Our results suggest that serum ferritin could be added to routine evaluation of metabolic syndrome patients; this would help identify a subgroup of individuals at risk for iron-related tissue damage (i.e., IR-HIO) (19), in whom further investigations may be appropriate. As a result, IR-HIO may be prevented by an inexpensive therapeutic approach such as phlebotomy therapy (14).

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