Body Iron Stores Are Associated With Serum Insulin and Blood Glucose Concentrations

Population study in 1,013 eastern Finnish men

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OBJECTIVE — To study if there is an association between mildly elevated body iron and glucose homeostasis indexes.

RESEARCH DESIGN AND METHODS — A cross-sectional population study was conducted in 1,013 middle-aged men, and an association of serum ferritin with concentrations of serum insulin, blood glucose, and serum fructosamine was tested.

RESULTS — The mean concentration of fasting serum insulin was 21.6% higher (95% CI 7.3–37.9%, $P < 0.001$) in the 5th quintile of serum ferritin compared with the 1st quintile. The elevation in blood glucose was 6.1% (95% CI 2.3–9.9%, $P < 0.001$) and in serum fructosamine 3.9% (1.5–6.9%, $P < 0.01$).

CONCLUSIONS — Mildly elevated body iron stores are associated with statistically significant elevations in glucose homeostasis indexes.

Liver cirrhosis and increasing fibrosis in the pancreas, leading to development of type II diabetes, are frequent consequences of excess accumulation of body iron. Thus 50% of transfusion-treated thalassemia patients have abnormal glucose tolerance (1) and up to 65% of hereditary hemochromatosis patients develop diabetes (2). Although iron accumulation has to be severe to induce organ damage that leads to diabetes, it appears plausible that even a lesser accumulation of iron can alter the glucose and insulin homeostasis of the body. To our knowledge, this association has not been studied in a randomly selected study population. For this reason, we tested the hypothesis that body iron stores are associated with blood insulin and glucose concentrations in a random sample of middle-aged men in eastern Finland.

RESEARCH DESIGN AND METHODS

Subjects

The study population consisted of the 4-year follow-up cohort of 1,038 men of the population-based Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), for which the sample was a random third of 42-, 48-, 54-, and 60-year-old men living in the district of Kuopio in eastern Finland. From the 3,235 invited, 2,682 (82.9%) participated. The 4-year follow-up cohort included all 1,229 subjects who had undergone carotid ultrasound examination at baseline. From the total 1,229 subjects, 1,038 (84.5%) participated. Both the baseline and the 4-year follow-up studies have been described in detail previously (3,4). All subjects with insulin therapy were excluded from the study. All measurements were available for total of 1,013 subjects.

Assessment of diabetes

A subject was defined diabetic if he had a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment or a positive finding in the oral glucose tolerance test (OGTT). The World Health Organization (WHO) criteria (5) were used to categorize subjects for having diabetes or impaired glucose tolerance (IGT), according to venous blood glucose concentrations.

Laboratory measurements

The laboratory measurements were made from fasting venous blood samples. Serum ferritin concentrations were measured from frozen serum samples using a radioimmunoassay (RIA) (Amersham International, Amersham, U.K.) based on a double antibody technique. Measurements of blood glucose were made from fresh whole-blood samples using the glucose dehydrogenase method (Granutest 100, Merck, Darmstadt, Germany). Serum insulin concentrations were determined from frozen serum samples with an RIA (Phasedeph Insulin, Pharmacia, Uppsala, Sweden). The measurements of serum fructosamine concentrations were made from frozen serum samples photometrically (Boehringer Mannheim, Mannheim, Germany) by an autoanalyzer (Kone Spesific, Kone Inc., Espoo, Finland). In the OGTT, an oral glucose load of 75 g in water solution was used.

Estimation of other variables

BMI, waist-to-hip ratio (WHR), alcohol consumption, and duration of conditioning physical activity were estimated as previ-

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FFA, free fatty acids; IGT, impaired glucose tolerance; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; OGTT, the oral glucose tolerance test; RIA, radioimmunoassay; WHO, The World Health Organization; WHR, waist-to-hip ratio.

Table 1—*Characteristics of the study population of 1,013 eastern Finnish men*

	Mean	SD	Minimum	Maximum
Age	56.2	6.7	46.4	65.4
Serum ferritin (μg/l)	148	124	12	1,300
Blood glucose (mmol/l)	5.1	1.2	3.1	17.5
Serum insulin (mU/l)	8.0	6.1	2.0	52.2
Serum fructosamine (μmol/l)	238	29	166	499
OGTT 2-h glucose (mmol/l)	5.9	2.8	2.1	25.9
OGTT 2-h insulin (mU/l)	51.9	50.7	2.0	552
BMI (kg/m^2)	27.5	3.6	19.5	41.8
WHR	0.99	0.04	0.80	1.12
Alcohol consumption (g/week)	80	118	0	1,104
Conditioning physical activity (h/week)	2.6	3.0	0	27.5

ously described (4,6). Present use of oral diabetes medication and of diuretics was dichotomized.

Statistical methods

The associations between serum ferritin and different indicators of glucose homeostasis were analyzed using Student's *t* test, Pearson's product-moment correlations, multivariate least-squares regression analysis, and one-way analysis of variance. Computations were performed with SPSS-X software for IBM RS/6000 computers.

RESULTS — The characteristics of the study population are presented in Table 1. Of the 1,013 participants, 75 (7.4%) had type II diabetes, 166 (16.4%) had impaired glucose tolerance (IGT), and 772 (76.2%) had normal glucose tolerance. Fifteen men (1.5%) had oral medication for diabetes, and 29 men (2.9%) had diuretic medication.

In regression models including all variables, serum ferritin in quintiles was the strongest determinant of serum fructosamine concentration, the second strongest determinant of blood glucose (after BMI), and the third strongest determinant of serum insulin and OGTT serum insulin and blood glucose. The two strongest determinants of these three were BMI and age.

The increase in blood glucose and serum insulin concentrations was detected in the two highest quintiles of serum ferritin, whereas serum fructosamine concentration was increased only in the highest quintile (Table 2). The difference between the highest and the lowest serum ferritin quintile was 6.1% (95% CI 2.3–9.9%, $P < 0.001$) for fasting blood glucose, 21.6% (95% CI 7.3–37.9%, $P < 0.001$) for fasting serum insulin, and 3.9% (95% CI 1.5–6.3%, $P < 0.01$) for fasting serum fructosamine. In the 2-hour measurement of oral glucose tolerance test, the insulin concentration increased fourfold (420%) in the lowest serum ferritin quintile and fivefold (532%) in the highest. The blood glucose concentration increased by 6.1 and 16.1%, respectively. The exclusion of subjects with a liver disease did not markedly affect the findings.

CONCLUSIONS — Our study demonstrates that increased body iron stores, as measured by serum ferritin concentration, were associated with elevated serum insulin, blood glucose, and serum fructosamine concentrations in middle-aged men in eastern Finland. The associations persisted as statistically significant after adjustment for the major determinants of glucose and insulin homeostasis.

Previous studies assessing the question whether moderately high body iron stores are associated with glucose homeostasis in type II diabetics have produced somewhat controversial results (7–10). However, these studies have been carried out in selected study samples, and the results may thus not be generalizable. Our study was carried out in a representative population sample of middle-aged men. The cross-sectional design, however, does not enable us to infer causality between body iron stores and insulin and glucose concentrations.

However, the high incidence of diabetes in hemochromatosis and the finding that parenterally administered iron can induce diabetes in animal models speak in favor of a causal association (2,11). Excess iron could theoretically be related to disturbed glucose homeostasis in at least three different ways. First, it could affect insulin synthesis and secretion in the pancreas (12,13). In this study, however, insulin secretion responded similarly to oral glucose load both in the highest and the lowest serum ferritin quintiles, suggesting that modest elevations in body iron do not affect pancreatic capacity to secrete insulin. Second, elevated body iron could enhance oxidation of lipids, especially of free fatty acids (FFA), through accelerated production of free radicals, as ferrous iron is a powerful catalyst. Increased FFA oxidation diminishes glucose utilization in muscle tissue and increases gluconeogenesis in the liver, leading to increased insulin resistance (12,13). In addition, accumulating iron could interfere with the insulin-extracting

Table 2—*The adjusted means and 95% CI of blood glucose, serum insulin, and serum fructosamine concentration in the quintiles of serum ferritin concentration in 1,013 men in eastern Finland*

Serum ferritin (μg/l)	≤57 (*n* = 211)	58–94 (*n* = 198)	95–142 (*n* = 205)	143–216 (*n* = 200)	>216 (*n* = 199)	*P* for trend
Blood glucose (mmol/l)	4.93 (4.85–5.02)	4.96 (4.84–5.07)	4.89 (4.80–4.99)	5.02 (4.92–5.13)	5.23 (5.06–5.39)	0.0001
Serum insulin (mU/l)	6.25 (5.76–6.78)	6.03 (5.52–6.60)	5.80 (5.30–6.36)	6.54 (5.97–7.18)	7.60 (6.91–8.37)	0.0002
Serum fructosamine (μmol/l)	233 (230–236)	235 (231–238)	236 (233–239)	236 (233–240)	242 (238–242)	0.0001
OGTT 2-h glucose (mmol/l)	5.23 (5.00–5.47)	5.29 (5.01–5.58)	5.21 (4.96–5.48)	5.50 (5.24–5.78)	6.07 (5.74–6.41)	<0.0001
OGTT 2-h insulin (mU/l)	32.5 (29.2–36.1)	33.3 (29.6–37.5)	31.1 (27.7–35.0)	39.0 (34.7–44.5)	48.0 (42.4–54.3)	<0.0001

Adjusted for age, examination year and season, family history of diabetes, BMI, WHR, alcohol consumption, conditioning leisure time physical activity, use of oral diabetes medication, and use of diuretics.

capacity of the liver (14). In our study, both blood glucose and serum insulin concentrations were elevated at mildly increased (>150 μg/l) serum ferritin concentrations. The elevation was more apparent in serum insulin concentration, a marker of insulin resistance (15). Supporting evidence for accumulating iron leading to development of insulin resistance comes from studies in noncirrhotic hemochromatotics and in hypertransfused betathalassemics (14,16).

Serum ferritin concentration is considered a good measure of body iron stores in healthy people (17). The gold standard of estimating body iron, liver biopsy, and evaluation of iron in the sample.is an invasive and risky method that cannot be used in population studies.

In conclusion, this study showed an independent positive association between serum ferritin concentration and markers of glucose homeostasis. Even though the observed elevations were not very large, they can be important for the population, from the public health point of view. However, the finding has to be confirmed in further studies. Among the large number of environmental and genetic factors contributing to the development of diabetes, excess body iron appears to be a potential new candidate.

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