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Original Article

Relationships of iron metabolism with insulin resistance and glucose levels in young and healthy adults

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ABSTRACT

Aims: Several biomarkers within the iron metabolism pathway have been related to the occurrence of diabetes mellitus, but underlying mechanisms are unknown. The aim of our study was to investigate the differential relationships of iron metabolism with a broad range of diabetes markers in young and healthy adults.
Design: 2160 participants aged 25 to 41 years were enrolled in a population-based study. Established cardiovascular disease, diabetes or a body mass index >35 kg/m^2 were exclusion criteria. Multivariable linear regression models were built to assess the associations of ferritin and transferrin saturation (TSAT) with blood levels of glucagon-like peptide-1 (GLP-1), insulin, homeostatic model assessment-insulin resistance (HOMA-IR), fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c).
Results: Median (interquartile range) age was 37 (31, 40) years. In multivariable linear regression analyses, β-coefficients (95% confidence intervals) per 1-SD increase in ferritin were 0.04 (0.02; 0.07, p = 0.0008) for GLP-1, 0.06 (0.04; 0.08, p < 0.0001) for insulin, 0.07 (0.04; 0.09, p < 0.0001) for HOMA-IR, 0.004 (−0.00; 0.01, p = 0.07) for FPG and −0.003 (−0.01; −0.00, p = 0.07) for HbA1c. β-coefficients (95% CI) per 1-SD increase in TSAT were −0.07 (−0.09; −0.05, p < 0.0001) for GLP-1, −0.06 (−0.08; −0.04, p < 0.0001) for insulin, −0.07(−0.09; −0.05, p < 0.0001) for HOMA-IR, −0.01 (−0.01; −0.00, p < 0.0001) for FPG and −0.01 (−0.01; −0.00, p = 0.0004) for HbA1c.
Conclusions: Markers of insulin resistance are strongly related with markers of iron metabolism in healthy subjects. These relationships were inconsistent and weaker for short-term and long-term glucose levels. These results may provide insights in the relationships between iron metabolism and diabetes occurrence.
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1. Introduction

Diabetes is a highly prevalent disease, a key risk factor for cardiovascular events and a major cause of a reduced lifespan [1–3]. Defining the causes and risk factors for diabetes occurrence is therefore a major public health priority.

The relationships of ferritin with risk of diabetes have been described previously [4–7], but the underlying pathophysiology is not completely understood [8]. A possible mechanism may be oxidative stress induced by increased iron deposition in beta- and liver cells, leading to cell damage and liver-mediated insulin resistance, higher insulin secretion and glucose dysregulation [9–11]. In return, insulin may facilitate iron overload by redistribution of transferrin receptors to the cell surface and cellular uptake forming a vicious cycle [12,13]. Only recently the role of transferrin saturation (TSAT) in this relation has been recognized, but no consistent relations with the occurrence of diabetes were found [14–18].

Ferritin is the standard marker for non-invasive evaluation of iron stores [19]. TSAT, by representing both serum iron and total iron-binding capacity, gives further valuable information about iron status [20]. In order to improve the knowledge on the relationship between

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment-insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; TSAT, transferrin saturation.

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body iron stores and glucose metabolism a thorough investigation including a broad range of markers related to both iron and glucose metabolisms is needed. Inclusion of glucagon-like peptide-1 (GLP-1), responsible for postprandial insulin response and improvement of insulin sensitivity [21,22], could give even further insights in this process and its relationships with other cardiovascular risk factors [23–25].

Therefore the aim of our study was to investigate the differential relationships of iron metabolism with a broad range of diabetes markers in a large and well defined cohort of young and healthy adults.

2. Material and methods

2.1. Study participants

Study subjects investigated in the current analysis take part in the ongoing genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors (GAPP) study. Detailed study information has been published previously [26]. In brief, 2170 inhabitants of the Principality of Liechtenstein were enrolled into a prospective cohort study between 2010 and 2013. Exclusion criteria were current intake of antidiabetic drugs, a body mass index (BMI) >35 kg/m^2, diagnosed cardiovascular disease or any other severe illnesses. We further excluded subjects with missing data on TSAT and/or ferritin levels (n = 10), such that 2160 subjects were used for the current analysis. The study protocol was approved by the local ethics committee and written informed consent was obtained from each participant.

2.2. Study variables

Standardized assessment of personal, medical, lifestyle and nutritional factors was performed using validated study questionnaires. Physical activity was determined with the validated IPAQ questionnaire [27]. Smoking behavior was classified by categorial indicator variables into current, past or never. Weight and height were directly measured in a standardized manner. BMI was calculated as body weight in kilogram divided by height in meter squared.

2.3. Blood biomarker assessment

Fasting venous blood samples were taken from each study subject, immediately centrifuged and stored at −80 °C. Plasma levels of fasting GLP-1 and insulin were assayed from frozen EDTA plasma samples, using a novel high-sensitive and single-molecule counting technology assay (Erenna Immunoassay System, Singulex, Alameda, CA, USA) [28]. Plasma levels of ferritin, TSAT and fasting plasma glucose (FPG) were analyzed on a Roche Cobas 6000 analyzer (F. Hoffmann — La Roche, Switzerland) and Hemoglobin A_{1c} (HbA1c) was measured by a high-performance liquid chromatography method (Biorad D10, Pratteln, Switzerland), all using fresh blood samples. homeostatic model assessment-insulin resistance (HOMA-IR) was calculated using the formula by Matthews et al. [29]. For the assessment of the glomerular filtration rate (GFR), we used the creatinine based chronic kidney disease epidemiology collaboration (CKD-EPI) formula [30].

All other biomarkers used in this analysis were assayed as described in detail previously [26].

2.4. Statistical analysis

Baseline characteristics were stratified by sex. The distribution of continuous variables was assessed using skewness, kurtosis and visual inspection of the histogram. These variables were presented as mean ± standard deviation or median (interquartile range), as

Table 1
Baseline characteristics according to sex.

	Male (n = 1011)	Female (n = 1149)	p-Value
Ferritin, μg/l	178 (114; 262)	46 (28; 79)	<.0001
TSAT, %	36 (28; 44)	32 (23; 41)	<.0001
Age, years	36.8 (31.4; 40.4)	36.7 (30.9; 40.1)	0.4
BMI, kg/m^2	25.6 (23.6; 27.9)	22.6 (20.6; 25.3)	<.0001
Smoking			0.0005
Current	256 (25.3)	221 (19.2)	
Past	245 (24.2)	260 (22.6)	
Never	509 (50.4)	666 (58.0)	
Alcohol intake, g/d	1.4 (0.0; 3.0)	0.0 (0.0; 0.8)	<.0001
Physical activity, min/week	180 (60; 450)	120 (30; 285)	<.0001
Education			<.0001
Low	66 (6.5)	107 (9.3)	
Medium	529 (52.3)	682 (59.4)	
High	388 (38.4)	336 (29.2)	
Office systolic BP, mm Hg	126.5 (120.0; 134.5)	112.5 (106.5; 119.5)	<.0001
Antihypertensive treatment	26 (2.6)	9 (0.8)	0.001
LDL-C, mmol/l	3.2 (2.6; 3.8)	2.6 (2.2; 3.1)	<.0001
HDL-C, mmol/l	1.3 (1.1; 1.5)	1.7 (1.5; 1.9)	<.0001
Triglycerides, mmol/l	1.0 (0.7; 1.5)	0.7 (0.6; 1.0)	<.0001
Fasting plasma glucose, mmol/l	5.0 (4.7; 5.3)	4.7 (4.4; 4.9)	<.0001
Hemoglobin A_{1c}, %	5.4 (5.2; 5.7)	5.4 (5.2; 5.6)	0.002
Insulin, mIU/l	6.5 (4.6; 9.7)	5.6 (4.2; 7.9)	<.0001
HOMA-IR	1.4 (1.0; 2.2)	1.2 (0.9; 1.7)	<.0001
GLP-1, ng/L	32.1 (24.2; 43.9)	31.3 (22.4; 41.2)	0.0006
Pro-BNP, ng/l	20.0 (11.0; 32.0)	50 (33.0; 80.0)	<.0001
Hs-CRP, mg/l	0.9 (0.5; 1.8)	0.9 (0.5; 2.1)	0.2
Hemoglobin, g/l	150 (144; 155)	130 (125; 136)	<.0001
Bilirubin, μmol/l	10.3 (7.4; 13.7)	8.6 (6.2; 12.0)	<.0001
Creatinine, μmol/l	76.9 (69.8; 84.9)	59.2 (53.0; 66.3)	<.0001
GFR, ml/min/1.73m^2	110.6 (101.7; 117.0)	113.1 (104.7; 119.4)	<.0001

p values were based on Mann–Whitney U tests or Chi-square tests, as appropriate. Data are median (interquartile range) or number (percentage).
BMI = body mass index; BP = blood pressure; GFR = glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HDL-C = high density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment-insulin resistance; Hs-CRP = high-sensitivity C-reactive protein; LDL-C = low density lipoprotein cholesterol; pro-BNP = N-terminal prohormone of brain natriuretic peptide.

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