Ferritin and Transferrin Are Both Predictive of the Onset of Hyperglycemia in Men and Women Over 3 Years

The Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study

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OBJECTIVE — The aim of the present work was to determine, in a cohort of men and women, whether ferritin and transferrin were associated with glucose metabolism and whether they were predictive of the onset of hyperglycemia (impaired fasting glycemia or type 2 diabetes) after 3 years of follow-up.

RESEARCH DESIGN AND METHODS — Among 4,501 subjects from the French Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort, 1,277 subjects (644 men and 633 women) were randomly selected for the analysis of iron biomarkers at baseline and at 3 years. In addition, to determine whether these parameters were relevant to pathological changes, all 231 subjects normoglycemic at baseline and hyperglycemic 3 years later were analyzed for iron biomarkers.

RESULTS — At baseline, plasma ferritin concentrations were positively correlated with fasting insulin and fasting glucose in the 1,277 subjects. Although transferrin and ferritin were negatively correlated, transferrin was also positively correlated with fasting insulinemia. Baseline ferritin concentration was an independent predictor of an increase in insulin concentration over a 3-year period ($P = 0.002$). Further, baseline ferritin and transferrin were independently associated with the onset of hyperglycemia over a 3-year period in the whole population ($P < 0.001$ for both) and in each sex.

CONCLUSIONS — Although negatively correlated, both transferrin and ferritin were positively associated with the onset of abnormalities in glucose metabolism in a prospective study. These results further support the hypothesis of a causative role of iron metabolism in the onset of insulin resistance and type 2 diabetes.

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Abbreviations: CRP, C-reactive protein; DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; IFG, impaired fasting glucose; WHR, waist-to-hip ratio.

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

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Several studies have reported an association between serum ferritin concentration and insulin resistance or type 2 diabetes (1), and it has been suggested that disturbances of iron metabolism are part of the metabolic syndrome, which associates insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, and central obesity (2). However, most of the observations come from cross-sectional or case-control studies and, until recently, it was not clear whether elevated iron stores predicted the risk of development of insulin resistance and type 2 diabetes among healthy individuals because there were few prospective studies. A recent large prospective study in healthy women showed that higher iron stores (reflected by ferritin concentrations and the ratio of transferrin receptors to ferritin) were associated with an increased risk of type 2 diabetes, independently of known diabetes risk factors (3). Transferrin was not measured in this study; however, it has been shown that transferrin is an important determinant of the lipolytic activity of human serum in adipocytes (4), and adipose tissue lipolysis has been recognized as a major determinant of insulin resistance (5). Thus, higher levels of transferrin, although usually negatively correlated with ferritin, could also be involved in the risk of insulin resistance and type 2 diabetes. The aim of the present work was to determine, in a prospective cohort with both men and women, whether biomarkers reflecting iron status (including both ferritin and transferrin) could predict the risk to develop changes in glucose metabolism in subjects who initially were normoglycemic.

RESEARCH, DESIGN AND METHODS

— The study population was men and women, aged 30–64 years, who participated in the cohort Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR), a 9-year follow-up study that aims to clarify the development of the insulin resistance syn-

Table 1— ***Pearson correlation coefficients between iron status parameters and other variables at baseline: the DESIR study***

	Plasma iron		Ferritin		Transferrin	
	r	*P*	*r*	*P*	*r*	*P*
All (N = 1,277)						
Insulin	−0.091	0.001	0.192	<0.0005	0.189	<0.0005
Glucose	0.070	0.012	0.279	<0.0005	0.009	0.758
BMI	−0.050	0.071	0.295	<0.0005	0.120	<0.0005
WHR	0.088	0.002	0.576	<0.0005	0.037	0.188
Age	0.008	0.767	0.210	<0.0005	−0.029	0.305
CRP	−0.192	0.000	0.042	0.136	0.047	0.094
Men (n = 644)						
Insulin	−0.099	0.012	0.244	<0.0005	0.175	<0.0005
Glucose	0.079	0.045	0.207	<0.0005	0.055	0.162
BMI	−0.059	0.133	0.251	<0.0005	0.186	<0.0005
WHR	0.001	0.990	0.244	<0.0005	0.187	<0.0005
Age	0.018	0.642	0.111	0.005	0.051	0.197
CRP	−0.202	<0.0005	0.013	0.749	−0.009	0.812
Women (n = 633)						
Insulin	−0.121	0.002	0.081	0.043	0.237	<0.0005
Glucose	−0.015	0.698	0.138	0.001	0.023	0.566
BMI	−0.109	0.006	0.193	<0.0005	0.126	0.001
WHR	−0.054	0.175	0.880	<0.0005	0.157	<0.0005
Age	−0.006	0.873	0.375	<0.0005	−0.096	0.016
CRP	−0.153	<0.0005	0.188	<0.0005	0.150	<0.0005

drome (6). Participants were recruited from volunteers insured by the French Social Security, which offers periodic health examinations free of charge. Subjects came from 10 health examination centers in western-central France. All subjects provided informed consent. The protocol was approved by the Comité Consultatif de la Protection des Personnes pour la Recherche Biomédicale of Bicêtre Hospital.

At baseline, 5,212 subjects were included, and 4,501 had a second examination 3 years later. Among them, 1,300 subjects (650 men and 650 women) were randomly selected for the analysis of iron metabolism parameters at both baseline and 3 years. Some of these subjects were excluded from the analyses due to one or more missing data.

In the whole DESIR cohort, 3,982 subjects who had both examinations were normoglycemic at baseline, with a fasting plasma glucose <6.1 mmol/l and not treated by antidiabetic agents. Among them, 231 were hyperglycemic at 3 years (200 with impaired fasting glucose [IFG], indicated by fasting plasma glucose between 6.1 and 6.9 mmol/l [7], and 31 with type 2 diabetes, indicated by plasma glucose ≥7.0 mmol/l or treatment with antidiabetic agents). All of these subjects had a determination of iron metabolism parameters, and they were compared with the 1,068 subjects from the randomly selected sample who remained normoglycemic. Very few subjects from the whole population included in the study had acute inflammation because only 3% had a C-reactive protein (CRP) concentration >10 mg/l.

Weight, height, and waist and hip circumferences were measured by trained personnel, and BMI (kilograms divided by the square of height in meters) and waist-to-hip ratio (WHR) were calculated. Venous blood samples were collected in the morning after subjects had fasted for 12 h. Fasting plasma glucose was assayed by the glucose-oxidase method applied to fluoro-oxalated plasma using a Technicon RA-1000 automatic analyzer (Bayer, Puteaux, France) or a Specific or a Delta analyzer (Konelab, Evry, France); fasting serum insulin was measured by an enzymoimmunoassay with the IMx system (Abbott, Rungis, France) (8).

Serum iron was measured by a spectrophotometric assay with ferrozine, and transferrin was assayed by turbidimetry using specific anti-human transferrin antibodies, both with commercially available kits (Thermo Clinical Labsystems, Oy, Finland) using an Optima 2000 analyzer (KONE, Evry, France). Ferritin was determined on a BN II nephelometer (Dade Behring, Marburg, Germany). Results are expressed in micrograms per liter. CRP was measured using a highly sensitive latex-enhanced immunonephelometric assay on a BN II nephelometer.

Univariate associations between continuous variables were tested by Pearson correlation coefficients. The associations between glycemic and iron status parameters at baseline and between baseline and 3 years were quantified by multiple linear regressions. Mean values at baseline were compared by ANOVA or ANCOVA adjusted for sex, age, and BMI. Hyperglycemia at 3 years was predicted by multiple logistic regressions. All independent variables, including iron-related parameters, CRP, and classic confounding factors, were incorporated in the same logistic regression equation to yield odds ratios (ORs) adjusted for all other variables. Skewed variables (BMI, insulin, ferritin, and CRP) were log transformed before statistical analyses. For the prediction of hyperglycemia risk, values of iron-related variables and CRP were replaced by standardized values (z-scores). Therefore, the ORs correspond to 1 SD increase for any of the parameters. For analyses, we used Systat for Windows (version 10) software.

RESULTS — In agreement with previous studies, we found significant correlations between iron parameters and parameters of glucose metabolism, age, BMI, WHR, and CRP in the studied population (Table 1). At baseline, ferritin and transferrin were independently and positively associated with fasting insulin, whereas iron was negatively associated, after adjusting on age, sex, BMI, WHR, and CRP (Table 2). Ferritin was positively associated with fasting glucose. Analysis by sex showed that all these results were observed in men, whereas in women, only the correlation between transferrin and insulin levels remained strongly significant, and the correlation between ferritin and insulin was only a trend.

Three-year longitudinal studies showed that baseline serum ferritin was an independent predictor of an increase in fasting insulin (P = 0.002) (Table 3) in the whole population. Analysis by sex showed that this result was only observed in women, whereas, in men, baseline transferrin was marginally associated with an increase in insulin.

In subjects normoglycemic at baseline, those who became hyperglycemic over the 3-year period had higher baseline

Table 2—*β-Coefficients from the multiple linear regression analysis of fasting insulin and fasting glucose at baseline: the DESIR study*

	Fasting insulin (μU/ml)	*P*	Fasting glucose (mmol/l)	*P*
All				
Iron (μmol/l)	−0.006 ± 0.002	0.002	0.001 ± 0.001	0.232
Ferritin (μg/l)	0.075 ± 0.017	<0.0005	0.018 ± 0.006	0.003
Transferrin (g/l)	0.213 ± 0.039	<0.0005	0.016 ± 0.013	0.239
BMI (kg/m^2)	1.400 ± 0.108	<0.0005	0.139 ± 0.038	<0.0005
WHR	1.115 ± 0.247	<0.0005	0.246 ± 0.086	0.004
Age (years)	−0.005 ± 0.001	<0.0005	0.001 ± 0.000	0.002
CRP (mg/l)	0.008 ± 0.018	0.661	0.006 ± 0.006	0.293
Female sex	0.185 ± 0.041	<0.0005	−0.019 ± 0.014	0.187
Men				
Iron (μmol/l)	−0.008 ± 0.003	0.004	0.002 ± 0.001	0.038
Ferritin (μg/l)	0.113 ± 0.026	<0.0005	0.032 ± 0.009	0.001
Transferrin (g/l)	0.174 ± 0.061	0.004	0.024 ± 0.022	0.261
BMI (kg/m^2)	1.589 ± 0.174	<0.0005	0.184 ± 0.062	0.003
WHR	1.228 ± 0.373	0.001	0.134 ± 0.133	0.315
Age (years)	−0.004 ± 0.002	0.062	0.002 ± 0.001	0.018
CRP (mg/l)	−0.011 ± 0.026	0.670	0.019 ± 0.009	0.035
Women				
Iron (μmol/l)	−0.004 ± 0.003	0.186	−0.000 ± 0.001	0.781
Ferritin (μg/l)	0.043 ± 0.024	0.073	0.008 ± 0.008	0.300
Transferrin (g/l)	0.218 ± 0.050	<0.0005	0.005 ± 0.017	0.762
BMI (kg/m^2)	1.254 ± 0.138	<0.0005	0.105 ± 0.047	0.026
WHR	0.933 ± 0.328	0.005	0.328 ± 0.112	0.004
Age (years)	−0.006 ± 0.002	0.005	0.002 ± 0.001	0.025
CRP (mg/l)	0.0361 ± 0.025	0.144	−0.002 ± 0.008	0.849

Data are coefficients ± SE.

values for metabolic syndrome parameters, CRP, ferritin, and transferrin (Table 4). When ferritin and transferrin were adjusted for CRP, these results remained unchanged, as well as when the few subjects with CRP >10 mg/l were excluded (data not shown), indicating that these results are not due to acute inflammation.

Multiple logistic regression analysis showed that baseline ferritin, transferrin, and CRP were independent predictors of the development of hyperglycemia after adjustment for the traditional risk factors for diabetes, including baseline glucose and insulin concentrations (Fig. 1). The results for ferritin and transferrin were significant in both men and women, but CRP was significantly associated with the onset of hyperglycemia in men only (Fig. 1). Again, when subjects with CRP >10 mg/l were excluded (data not shown), results remained the same.

CONCLUSIONS — We have confirmed the previously reported association between plasma ferritin and markers of glucose metabolism (1). In the 3-year prospective analysis, ferritin was an independent predictor of an increase in fasting insulin, mainly in women. This observation was confirmed to be relevant to the development of hyperglycemia in a nested study, which included all subjects in the DESIR study who were normoglycemic at baseline and had either IFG or diabetes at the 3-year follow-up. These results were observed in both men and women. Because ferritin is not only a marker of iron load but is also increased in inflammatory states, it was important to include CRP in the multivariate analysis. In agreement with a previous report in women, it appears from our study that ferritin predicts the development of IFG of diabetes independently of CRP, sug-

Table 3—*β-Coefficients from the multiple linear regression analysis of glucose metabolism in the 3-year longitudinal study: the DESIR study*

	Change in insulin (μU/ml)	*P*	Change in glucose (mmol/l)	*P*
All*				
Iron (μmol/l)	−0.002 ± 0.002	0.181	0.001 ± 0.000	0.245
Ferritin (μg/l)	0.050 ± 0.016	0.002	0.004 ± 0.004	0.343
Transferrin (g/l)	0.060 ± 0.036	0.097	0.015 ± 0.010	0.110
Men†				
Iron (μmol/l)	−0.004 ± 0.003	0.180	0.001 ± 0.001	0.292
Ferritin (μg/l)	0.037 ± 0.025	0.137	0.010 ± 0.007	0.140
Transferrin (g/l)	0.110 ± 0.057	0.052	0.025 ± 0.015	0.105
Women†				
Iron (μmol/l)	−0.002 ± 0.003	0.477	0.000 ± 0.001	0.604
Ferritin (μg/l)	0.074 ± 0.022	0.001	0.002 ± 0.006	0.705
Transferrin (g/l)	0.050 ± 0.047	0.285	0.009 ± 0.012	0.468

Data are coefficients ± SE. *Independent baseline variables included in the regression models were iron, ferritin, transferrin, insulin, glucose, BMI, WHR, age, CRP, and sex. †Independent baseline variables included in the regression models were iron, ferritin, transferrin, insulin, glucose, BMI, WHR, age, and CRP.

Table 4—*Characteristics at entry according to glycemic status 3 years later in subjects who were initially normoglycemic: the DESIR study*

	Normoglycemic	IFG	Type 2 diabetes	*P* (sex adjusted)*	*P* (sex, age, and BMI adjusted)†
All					
N	1,068	200	31		
Percent men	46	69	58		
Age (years)	46.6 ± 9.9	49.2 ± 9.1	47.3 ± 8.9	<0.0005	
BMI (kg/m^2)	23.8 (21.8–26.4)	26.3 (24.2–28.5)	27.4 (23.8–31.6)	<0.0005	<0.0005
WHR	0.843 ± 0.088	0.900 ± 0.075	0.893 ± 0.095	<0.0005	<0.0005
Insulin (μU/ml)	5.3 (3.8–7.5)	6.9 (4.8–9.8)	6.4 (5.2–11.2)	<0.0005	<0.0005
Glucose (mmol/l)	5.17 ± 0.44	5.61 ± 0.39	5.50 ± 0.50	<0.0005	<0.0005
Iron (μmol/l)	19.3 ± 6.7	19.9 ± 6.2	19.0 ± 8.0	0.888	0.445
Ferritin (μg/l)	93 (42–175)	167 (102–169)	166 (68–353)	<0.0005	<0.0005
Transferrin (g/l)	2.31 ± 0.35	2.41 ± 0.28	2.49 ± 0.33	<0.0005	<0.0005
CRP (mg/l)	0.85 (0.85–2.07)	1.36 (0.92–2.91)	1.66 (0.98–3.85)	<0.0005	0.007
Men					
n	490	132	18		
Age (years)	46.4 ± 10.2	48.2 ± 8.7	48.2 ± 8.0	0.159	
BMI (kg/m^2)	24.7 (23.0–27.1)	26.5 (24.3–28.7)	28.1 (24.4–30.1)	<0.0005	<0.0005
WHR	0.912 ± 0.061	0.932 ± 0.056	0.953 ± 0.066	<0.0005	0.258
Insulin (μU/ml)	5.4 (3.8–7.7)	6.9 (4.7–9.4)	7.3 (5.5–11.3)	<0.0005	0.031
Glucose (mmol/l)	5.33 ± 0.41	5.64 ± 0.37	5.56 ± 0.40	<0.0005	<0.0005
Iron (μmol/l)	20.4 ± 6.5	20.4 ± 6.0	20.8 ± 9.1	0.969	0.881
Ferritin (μg/l)	169 (109–264)	209 (138–307)	270 (171–442)	<0.0005	0.004
Transferrin (g/l)	2.26 ± 0.30	2.36 ± 0.28	2.46 ± 0.31	<0.0005	0.009
CRP (mg/l)	0.85 (0.85–1.89)	1.36 (0.92–2.68)	1.50 (0.92–11.7)	0.001	0.023
Women					
n	578	68	13		
Age (years)	46.7 ± 9.7	51.0 ± 9.5	45.9 ± 10.1	0.002	
BMI (kg/m^2)	23.1 (20.9–25.4)	25.7 (23.8–28.3)	27.2 (21.4–32.6)	<0.0005	<0.0005
WHR	0.784 ± 0.061	0.838 ± 0.068	0.809 ± 0.057	<0.0005	<0.0005
Insulin (μU/ml)	5.1 (3.7–7.2)	7.0 (5.1–11.0)	5.5 (4.3–8.8)	<0.0005	<0.0005
Glucose (mmol/l)	5.02 ± 0.46	5.58 ± 0.39	5.40 ± 0.39	<0.0005	<0.0005
Iron (μmol/l)	18.4 ± 6.8	18.9 ± 6.5	16.5 ± 5.7	0.487	0.450
Ferritin (μg/l)	49 (29–88)	97 (47–164)	67 (34–111)	<0.0005	0.003
Transferrin (g/l)	2.35 ± 0.39	2.50 ± 0.27	2.54 ± 0.37	0.001	0.005
CRP (mg/l)	0.87 (0.85–2.19)	1.32 (0.92–3.81)	1.85 (1.38–5.57)	0.001	0.173

Data are means ± SD or median (25–75%) values. For all skewed variables (BMI, insulin, ferritin, and CRP), statistics were performed on log-transformed values. Normoglycemic: fasting plasma glucose <6.1 mmol/l; IFG: fasting plasma glucose between 6.1 and 7 mmol/l; type 2 diabetes: fasting glucose ≥7.0 mmol/l or treated for diabetes. *Measured by ANCOVA except χ^2 for the difference in sex frequency. †Measured by ANCOVA; BMI was only adjusted for sex and age.

gesting that the iron status itself may be involved. Iron is a catalyst in the formation of hydroxyl radicals, which are powerful prooxidants that attack cellular membrane lipids, proteins, and nucleic acids (9). Therefore, it has been hypothesized that the formation of hydroxyl radicals catalyzed by iron contributes initially to insulin resistance and subsequently to the development of type 2 diabetes. The results of one study on euglycemic-hyperinsulinemic and hyperglycemic clamps support the hypothesis of elevated iron stores as an etiological factor in insulin resistance rather than in β-cell dysfunction (10).

The main new finding in our study concerns transferrin. First, we observed a positive correlation between plasma transferrin concentrations and fasting insulin, WHR, and BMI. This observation may be explained, at least in part, by the previously reported upregulation of transferrin production by insulin in human hepatocytes (11). Secondly, a higher plasma transferrin level was also an independent predictor of the development of insulin resistance in the 3-year follow-up. This novel finding is intriguing because, in the DESIR population, as in the other populations, plasma transferrin was negatively correlated with plasma ferritin ($r = -0.289$, $P < 0.001$); a high iron load is reflected by high ferritin levels but decreased transferrin levels. Little is known about the regulation of transferrin (12). Plasma transferrin itself may be involved in the pathogenesis of insulin resistance because Vargas et al. (13) have shown an antagonist effect of human transferrin on insulin action. Moreover, it has recently been shown that transferrin is a major determinant of the lipolytic activity of human serum in adipocytes (4). An increase in adipose tissue lipolysis due to higher transferrin levels could increase availability of free fatty acids to the liver and skeletal muscle, which could in turn lead to insulin resistance (5).

In summary, both ferritin and transferrin levels were associated with hyperinsulinemia and hyperglycemia. Baseline ferritin and transferrin were independently predictive of development of hyperglycemia (IFG or type 2 diabetes) over a 3-year period. Prospective studies on blood donors indicated that

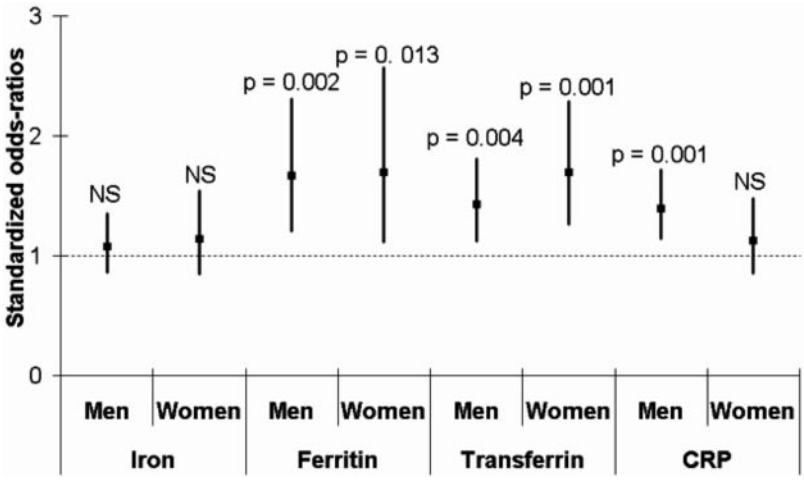

Figure 1—*Standardized ORs for the 3-year incidence of hyperglycemia (IFG or type 2 diabetes) according to baseline iron biomarkers and CRP (independent variables) after adjustment for baseline age, BMI, WHR, and glucose and insulin concentrations in the DESIR study. (All independent variables and adjustment variables were included in the same multiple logistic regression equation.)*

depletion of iron stores may prevent the development of insulin resistance (14,15) although other studies failed to report such an effect (16). Our present findings favor a causal role for iron metabolism on the onset of insulin resistance in both sexes. Accordingly, it may be suggested that differences in iron metabolism contribute at least in part to explain the higher prevalence of IFG and type 2 diabetes in male subjects. Further intervention studies are needed to evaluate the potential benefits of drawing blood in subjects at risk of developing insulin resistance.

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APPENDIX

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