Circulating Soluble Transferrin Receptor According to Glucose Tolerance Status and Insulin Sensitivity

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OBJECTIVE — The relationships between iron metabolism and type 2 diabetes are bidirectional: iron affects glucose metabolism and glucose metabolism impinges on several iron metabolic pathways. The mechanisms of these interactions depend on poorly known factors. We aimed to study the contribution of the serum soluble transferrin receptor (sTfR).

RESEARCH DESIGN AND METHODS — Circulating sTfR was evaluated in 221 men (97 with normal glucose tolerance [NGT], 36 with impaired glucose tolerance, and 88 with type 2 diabetes). In a subset of these subjects, glucose tolerance (oral glucose tolerance test [OGTT]), minimal model–derived insulin sensitivity, and sTfR during the OGTT were also evaluated.

RESULTS — Men with altered glucose tolerance showed significantly increased sTfR (9.4 ± 4.4 vs. 8.2 ± 2.6 μg/ml, $P = 0.02$) and higher serum ferritin than men with NGT. Serum sTfR was negatively associated with serum ferritin ($r = -0.16$, $P = 0.02$). sTfR correlated with several clinical and metabolic variables such as systolic blood pressure, glycated hemoglobin, and glucose and insulin values during OGTT. Insulin sensitivity was also negatively associated with sTfR in NGT and nonobese subjects. BMI ($P = 0.01$), serum ferritin ($P = 0.025$), and insulin sensitivity ($P < 0.0001$) contributed independently to 21% of sTfR variance. Serum sTfR concentration did not significantly change during the OGTT.

CONCLUSIONS — Both insulin sensitivity and glucose tolerance status are significantly associated with serum sTfR concentrations, although insulin sensitivity predicts independently circulating sTfR, mainly in subjects with NGT. The implications of the interrelationships between iron and glucose metabolism should be investigated further.

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Insulin is an anabolic hormone that stimulates the cellular uptake of many nutrients, including hexoses, amino acids, cations, and anions. In the steady state, iron circulates bound to transferrin and is taken up from the blood by a high-affinity specific transferrin receptor (TfR) (1). The TfR complex is internalized by endocytosis and released into a nonacidic cellular compartment, where it can be used in the synthesis of essential cellular components. Insulin is known to cause a rapid and marked stimulation of iron uptake by fat cells, redistributing TfRs from an intracellular membrane compartment to the cell surface (2). Insulin also induces iron transport and accumulation in hepatocytes by a similar mechanism (2) and is responsible for increased ferritin synthesis in cultured rat glioma cells (3). TfRs have been shown to colocalize with insulin-responsive glucose transporters and IGF-II receptors in the microsomal membranes of cultured adipocytes, suggesting that regulation of iron uptake by insulin parallels its effects on glucose transport (4).

The synthesis of TfR and the iron storage protein ferritin is regulated reciprocally at the posttranscriptional level according to the cellular iron status (5). As a result of the externalization of TfR during the endocytic cycle, a soluble form of TfR can be detected in serum (serum TfR [sTfR]). Circulating sTfR concentrations are proportional to cellular expression of the membrane-associated TfR (6). sTfR concentration is closely related to cellular iron demands; hence, the higher the ferritin level, the lower the sTfR concentration.

In a recent study, increased serum ferritin levels were found in type 2 diabetic patients in the absence of a reciprocal decrease of sTfR (7). This finding suggested to the authors that elevated ferritin levels in type 2 diabetes was due to inflammatory mechanisms rather than iron overload. However, they also observed higher sTfR levels in type 2 diabetic patients treated with insulin than in those treated with oral agents (7).

These observations are important because emerging scientific evidence has disclosed unsuspected influences between iron metabolism and type 2 diabetes (8). Increased iron stores have been found to predict the development of type 2 diabetes, whereas iron depletion seems protective. The mechanisms of these interactions depend on poorly known factors (8).

Thus, the aim of this study was to evaluate the possible associations among insulin resistance, insulin secretion, metabolic variables, and serum sTfR concentration after controlling for iron status.

RESEARCH DESIGN AND METHODS

— A total of 221 Caucasian men were recruited and studied. There were 153 of them recruited in an ongoing study dealing with nonclassical cardiovascular risk factors in Northern

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Abbreviations: IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; sTfR, serum transferrin receptor; TfR, transferrin receptor.

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

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Spain. Subjects were randomly localized from a census and were invited to participate. The participation rate was 71%. A 75-g oral glucose tolerance test (OGTT) according to the American Diabetes Association criteria was performed in all subjects. All subjects with normal glucose tolerance (NGT) ($n = 97$) had fasting plasma glucose <7.0 mmol/l and 2-h postload plasma glucose <7.8 mmol/l after a 75-g OGTT. Impaired glucose tolerance (IGT) was diagnosed in 36 subjects according to the American Diabetes Association criteria (postload glucose between 7.8 and 11.1 mmol/l). Previously unknown type 2 diabetes was diagnosed in 20 of these 153 subjects (postload glucose >11.1 mmol/l). Inclusion criteria were *1*) BMI <40 kg/m^2, *2*) absence of systemic disease, *3*) absence of infection within the previous month, and *4*) serum ferritin >10 ng/ml and normal blood hemoglobin concentration (>12 g/dl) to exclude iron deficiency. None of the control subjects were under medication or had evidence of metabolic disease other than obesity. Alcohol and caffeine were withheld within 12 h of performing the insulin sensitivity test. Smokers were defined as any person consuming at least one cigarette a day in the previous 6 months. Resting blood pressure was measured as previously reported (9–11). Liver disease and thyroid dysfunction were specifically excluded by biochemical workup.

To increase the statistical power of the group of patients with type 2 diabetes, 68 patients were prospectively recruited from diabetes outpatient clinics on the basis of a stable metabolic control in the previous 6 months, as defined by stable A1C values. Data from these patients were merged with those from the recently diagnosed type 2 diabetic patients. Exclusion criteria for these patients included the following: *1*) clinically significant hepatic, neurological, endocrinologic, or other major systemic disease, including malignancy; *2*) history or current clinical evidence of hemochromatosis; *3*) history of drug or alcohol abuse, defined as >80 g/day in men and >40 g/day in women, or serum transaminase activity more than twice the upper limit of normal; *4*) an elevated serum creatinine concentration; *5*) acute major cardiovascular event in the previous 6 months; *6*) acute illnesses and current evidence of acute or chronic inflammatory or infective diseases; and *7*) mental illness rendering the subjects unable to understand the nature, scope, and possible consequences of the study. Pharmacological treatment for these patients was as follows: insulin: 29 patients; metformin: 35 patients; sulfonylureas: 14 patients; statins: 28 patients; fibrates: 9 patients; blood pressure–lowering agents: 32 patients; aspirin: 32 patients; and allopurinol: 3 patients. All subjects gave written informed consent after the purpose of the study was explained to them. The institutional review board of the institution approved the protocol.

Anthropometric and clinical measurements

BMI was calculated as weight (in kilograms) divided by height (in meters) squared. The subjects waist was measured with a soft tape midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteal region. The waist-to-hip ratio was then calculated.

Study of insulin sensitivity

In those subjects who agreed (60 with NGT, 28 with IGT, and 7 patients with type 2 diabetes), insulin sensitivity was measured using the frequently sampled intravenous glucose tolerance test with minimal model analysis. In brief, the experimental protocol started between 8:00 and 8:30 A.M. after an overnight fast. A butterfly needle was inserted into an antecubital vein, and patency was maintained with a slow saline drip. Basal blood samples were drawn at −30, −10, and −5 min, after which glucose (300 mg/kg body wt) was injected over 1 min starting at time 0, and insulin (0.03 units/kg; Actrapid, Novo, Denmark) was administered at time 20. Additional samples were obtained from a contra-lateral antecubital vein up to 180 min, as previously described (9,10).

Analytical methods

Serum glucose concentrations were measured in duplicate by the glucose oxidase method using a Beckman glucose analyzer II (Beckman Instruments, Brea, CA). Total serum cholesterol was measured through the reaction of cholesterol esterase/cholesterol oxidase/peroxidase. Total serum triglycerides were measured through the reaction of glycerol-phosphate-oxidase and peroxidase. A1C was measured by the high-performance liquid chromatography method (Bio-Rad [Muenchen, Germany] and autoanalyzer Jokoh HS-10). Intra- and interassay coefficients of variation were <4% for all these tests.

Serum insulin levels were measured in duplicate by monoclonal immunoradiometric assay or enzyme-amplified sensitivity immunoassay (Medgenix Diagnostics, Fleunes, Belgium). Intra- and interassay coefficients of variation were similar to those previously reported (9,10).

Serum C-reactive protein (ultrasensitive assay; Beckman, Fullerton, CA) was determined by a routine laboratory test, with intra- and interassay coefficients of variation <4%. The lower limit of detection is 0.02 mg/l.

Serum soluble TfR was measured using a double monoclonal sandwich enzyme immunoassay (Biovendor, Palacheho tr., Brno, Czech Republic). Intra- and interassay coefficients of variation were <4.5%.

Statistical analysis

Descriptive results of continuous variables are expressed as mean (SD). Before statistical analysis, normal distribution and homogeneity of the variances were evaluated using Levene's test, and then variables were given a base 10 log-transformation if necessary. These parameters (ferritin, C-reactive protein, postload insulin, insulin sensitivity [S_I], and triglycerides) were analyzed on a log scale and tested for significance on that scale. The anti–log-transformed values of the means (geometric mean) are reported in the tables for this article. Relation between variables was tested using Pearson's test (with log-transformed values) and multiple linear regression analysis. We used unpaired *t* tests and the ANOVA test with Bonferroni's post hoc analysis for comparisons of quantitative variables. General linear model for repeated measures with Bonferroni's correction was used to compare sTfR levels during OGTT. The statistical analyses were performed using the program SPSS (version 12.0).

RESULTS — Characteristics of the subjects and the comparisons among groups are shown in Table 1. Subjects with IGT or type 2 diabetes were significantly older, were heavier, and showed lower insulin sensitivity than subjects with NGT.

We observed no differences in serum sTfR or ferritin among groups. However, subjects with altered glucose tolerance (i.e., with IGT or type 2 diabetes) showed significantly increased sTfR (9.4 ± 4.4 vs. 8.2 ± 2.6 μg/ml, $P = 0.02$) and increased

Table 1—*Anthropometrical and biochemical variables of the study subjects*

	NGT	IGT	Type 2 diabetes	*P* (ANOVA)
n (men)	97	36	88	—
Age (years)	49.5 ± 11.4*	57.8 ± 8.9	58.4 ± 10.2	<0.0001
BMI (kg/m^2)	26.9 ± 3.9†	28.4 ± 3.3	28.9 ± 3.9	<0.0001
Waist-to-hip ratio	0.91 ± 0.06†‡	0.95 ± 0.07§	1 ± 0.08	<0.0001
Systolic blood pressure (mmHg)	123.7 ± 15.06†‡	132.9 ± 16.5	142.2 ± 19.6‡	<0.0001
Diastolic blood pressure (mmHg)	78.9 ± 9.7‡	83.8 ± 8.7	82.4 ± 10.8	0.012
Fasting glucose (mmol/l)	5.23 ± 0.5	5.67 ± 0.6	9.4 ± 4.2*	<0.0001
Fasting insulin (mU/l)	8.4 ± 4.4‖	12.1 ± 5.9	11 ± 7.3¶	<0.002
120′ OGTT glucose (mmol/l)	5.98 ± 1.1*	9.07 ± 0.96*	13.2 ± 2.2	<0.0001
120′ OGTT insulin (mU/l)	30.6 (20.4–52.5)‖	96.4 (61.2–178.3)	52.1 (37–96)	<0.0001
A1C (%)	4.83 ± 0.51	4.85 ± 0.42	7.1 ± 1.7*	<0.0001
HDL cholesterol (mg/dl)	53.3 ± 13.8	50.4 ± 10.9	47.4 ± 12.7	0.009
Triglycerides (mg/dl)	81.5 (62.2–106)‡	110.5 (80.5–156.5)	181 (122.5–279)*	<0.0001
Insulin sensitivity (10^{-4} · mU/l)#	3.00 (2.19–4.8)*	1.25 (0.87–2.38)	0.8 (0.61–2.48)	<0.0001
sTfR (μg/ml)	8.1 ± 2.5**	9.5 ± 2.5	8.9 ± 3.8	0.055††
Transferrin (ng/ml)	246.8 ± 50.3	243.3 ± 69	257.8 ± 50	0.3
Ferritin (ng/ml)	135 (88.9–220)	147.9 (97.8–243.4)	149 (91.1–362.3)	0.1
C-reactive protein (mg/l)	0.2 (0.12–0.4)†‡	0.2 (0.13–0.51)	0.3 (0.23–0.8)	0.002

Data are means ± SD or median (interquartile range). *$P < 0.0001$ compared with the other two groups in post-hoc analysis. †P between 0.01 and <0.0001 compared with the type 2 diabetic group in post-hoc analysis. ‡$P < 0.05$ compared with the IGT group in post-hoc analysis. §$P < 0.05$ compared with the type 2 diabetic group in post-hoc analysis. ‖P between 0.01 and <0.0001 compared with the IGT group in post-hoc analysis. ¶Measured in all subjects except 68 patients with type 2 diabetes. #Measured in 60 subjects with NGT, 28 with IGT, and 7 with previously unknown type 2 diabetes. **$P = 0.07$ compared with the IGT group. ††$P = 0.002$ when considering nonobese subjects (then the numbers were 8.2 ± 2.3 in the NGT group, 11.2 ± 5.2 in the IGT group, and 9.3 ± 4.2 in the type 2 diabetic group; $P = 0.003$ in IGT group when compared with the NGT group in post-hoc analysis).

serum log ferritin (2.3 ± 0.37 vs. 2.2 ± 0.34, $P = 0.04$). When considering nonobese subjects separately, IGT subjects showed significantly increased serum sTfR concentration compared with the NGT group (Table 1, legend ††).

Serum sTfR was negatively associated with serum ferritin ($r = -0.16$, $P = 0.02$). Interestingly, sTfR also correlated with several clinical and metabolic variables such as systolic blood pressure, glycated hemoglobin and glucose and insulin values during the OGTT, and C-reactive protein (Table 2). The best association was observed with serum glucose and insulin 30′ after OGTT. However, this latter association was significant in subjects with NGT but not in those with altered glucose tolerance ($r = 0.35$, $P = 0.001$, Fig. 1). Insulin sensitivity was also negatively associated with sTfR in normal ($r = -0.30$, $P = 0.02$) but not in subjects with altered glucose tolerance. Obesity status also influenced these results. Insulin sensitivity correlated negatively with sTfR in nonobese subjects ($r = -0.49$, $P < 0.0001$, $n = 70$), but not in obese subjects ($r = -0.19$, $P = 0.3$). However, probably because of the low number of obese subjects, we could not detect significant differences in the correlation coefficients between obese and nonobese subjects ($P = 0.19$).

We performed a multiple linear regression analysis to predict circulating sTfR. We considered as independent variables those with significant association on univariant analysis. As shown in supplemental Table S1 (please see the online appendix at http://dx.doi.org/10.2337/dc06-1138), BMI ($P = 0.01$), serum ferritin ($P = 0.025$), and insulin sensitivity ($P < 0.0001$) contributed independently to 21% of sTfR variance, after controlling for the effects of age, systolic blood pressure, and serum insulin 30′ post-OGTT.

Among type 2 diabetic patients, individuals treated with insulin ($n = 29$) showed a tendency toward increased sTfR concentration (11.4 ± 7.4 vs. 8.5 ± 3.2

Table 2—*Correlations between circulating soluble TfR and clinical and biochemical variables*

	All subjects* ($n = 221$)	*P*
Age	0.12	0.08
BMI	0.10	0.1
Waist†	0.03	0.6
Systolic blood pressure	**0.15**	**0.02**
Diastolic blood pressure	0.11	0.09
Fasting glucose	0.13	0.12
30′ OGTT	**0.21**	**0.01**
120′ OGTT	**0.17**	**0.04**
A1C	**0.14**	**0.03**
Fasting insulin	0.12	0.1
30′ OGTT insulin	**0.19**	**0.02**
120′ OGTT insulin	0.08	0.3
Triglycerides	0.005	0.9
HDL cholesterol	0.01	0.7
S_I	**−0.32**	**0.001**
C-reactive protein	**0.18**	**0.01**

*OGTT was performed in 138 subjects; 30′, 60′, 90′, and 120′ indicate the minutes after glucose intake. †Waist was negatively correlated with sTfR in subjects with altered glucose tolerance ($r = -0.26$; $P = 0.04$). Bold values are statistically significant.

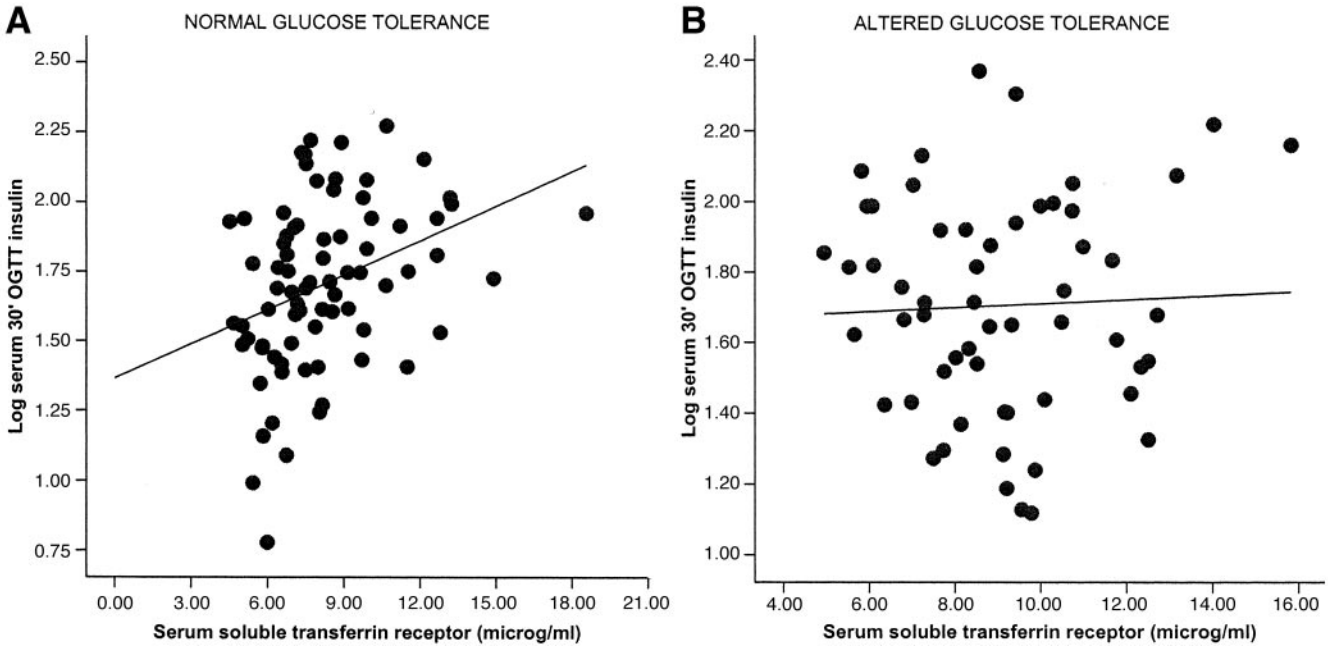

Figure 1—*Relationship between serum insulin 30′ during the OGTT and circulating soluble TfR in subjects with normal* (A) *and altered glucose tolerance* (B). *In the left panel, the relationship persisted significant after excluding the outlier with the lowest 30-min insulin* (r = *0.33,* P = *0.004), and after excluding both this outlier and the subject with the highest serum soluble TfR* (r = *0.32,* P = *0.005).*

μg/ml, $P = 0.057$) and similar log serum ferritin concentrations (2.1 ± 0.5 vs. 2.14 ± 0.4, $P = 0.3$). Patients treated with sulfonylureas ($n = 14$) also showed significantly increased sTfR concentrations (9.8 ± 3.4 vs. 7.0 ± 2.7 μg/ml, $P = 0.02$). Patients treated ($n = 35$) and untreated with metformin showed nonsignificantly different serum sTfR concentrations (9 ± 4.2 vs. 10.1 ± 6 μg/ml, $P = 0.2$). Four patients were treated with insulin and metformin, and three patients were treated with sulfonylureas and metformin concomitantly. Inclusion or exclusion of these subjects in the analysis did not significantly change the results.

Known patients with type 2 diabetes (duration of diabetes 7 ± 3 years), in contrast to newly diagnosed type 2 diabetic patients, had increased A1C values (6.9 ± 1.3 vs. 5.0 ± 0.9, for known and new type 2 diabetic patients, respectively; $P < 0.0001$). Duration of diabetes had no significant influence on serum sTfR concentration. When evaluating the relationship between serum sTfR concentration and glycated hemoglobin separately in type 2 diabetic patients, we did not find any significant association ($r = 0.15$, $P = 0.12$). However, obesity status and treatment influenced the relationship between sTfR concentration and glycated hemoglobin. These parameters were significantly associated in lean subjects ($r = 0.59$, $P = 0.04$, $n = 12$), in subjects not treated with insulin ($r = 0.30$, $P = 0.02$, $n = 59$), in patients receiving statins ($r = 0.49$, $P = 0.01$, $n = 28$), and in patients receiving aspirin ($r = 0.36$, $P = 0.04$, $n = 32$). In patients receiving insulin or sulfonylureas, these associations were not significant.

Study of acute regulation by insulin

To investigate the possible mechanisms of increased sTfR, we evaluated sTfR during OGTT in eight subjects (aged 55.2 ± 9.2 years, BMI 26.5 ± 1.9 kg/m^2). Serum sTfR concentration did not significantly change during the OGTT (sTfR concentration was 10.89 ± 1.9 μg/ml at baseline and remained essentially unchanged during the test). In this study, the best association was shown between insulin at 30 min during the OGTT and sTfR at 60 min ($r = 0.83$, $P = 0.01$).

CONCLUSIONS — Serum sTfR represents a soluble fragment of the extracellular receptor domain. Extensive previous studies indicate that, if iron deficiency is excluded (as was the case in all subjects studied), the level of serum receptors provides a quantitative measure of total erythropoiesis (6). TfR is expressed in a limited number of sites—notably immature erythroid cells, Kupffer cells, hepatocytes, testis, the pituitary gland, and the endocrine pancreas (12). In this article, we provide evidence according to which insulin sensitivity and insulin secretion are important factors influencing serum sTfR concentrations.

Serum sTfR concentrations were associated with acute insulin stimulation during OGTT (insulin levels 30′ after OGTT). Insulin is known to cause a rapid and marked stimulation of iron uptake by fat cells, redistributing TfRs from an intracellular membrane compartment to the cell surface (2). TfRs have been shown to colocalize with insulin-responsive glucose transporters in cultured adipocytes, suggesting that regulation of iron uptake by insulin parallels its effects on glucose transport. The effects of insulin increasing TfR have been observed in a myeloid leukemia cell line and mouse mammary gland cells (13). It has also been demonstrated that insulin injections increase sTfR in rats (14). Hyperinsulinemia may contribute to the inappropriately high sTfR concentration detected in subjects with altered glucose tolerance.

Serum sTfR concentrations seem not acutely regulated by insulin in humans, given the unaltered serum sTfR levels during the OGTT. This finding hints at a long-term regulation by insulin sensitivity. We cannot exclude, however, acute effects with prolonged insulin infusions. Insulin sensitivity, independently of age, obesity, and iron status, contributed independently to sTfR variance (supplemental Table S1). We observed that the lower the

insulin sensitivity, the higher the sTfR concentration, but only in subjects with NGT. Thus, subjects with altered glucose tolerance and type 2 diabetic patients not treated with aspirin or statins (see below) have in common some underlying factors that disrupt this relationship. In this sense, we were intrigued for the positive association between C-reactive protein and serum sTfR concentration. Different cytokines upregulate TfR expression in in vitro models (15,16). It is possible that different inflammatory factors lead to a spurious increase in serum sTfR in subjects with altered glucose tolerance and that treatment with aspirin or statins correct to some extent this increase.

Our findings are in agreement with those described by Hernández et al. (7), who described increased sTfR concentration in those type 2 diabetic patients treated with insulin. In this study, we also found that those patients treated with insulin or with sulfonylureas had significantly higher sTfR concentration. Furthermore, we found that concomitant treatment also influenced the association between serum sTfR concentration and glycated hemoglobin. Again, a spurious increase in sTfR in patients treated with insulin could obscure the relationship between sTfR and glycated hemoglobin. Although factors related to hyperglycemia or oxidative stress could mediate in part this association, increased A1C may also reflect a more severe insulin resistance (17). As found in nondiabetic subjects, the relationship between A1C and sTfR was significant in those subjects with less interference with inflammatory factors: lean subjects and patients receiving aspirin or statins.

Other possibilities cannot be excluded. Exposure of newborn rats to hypoxia leads to a significant increase in TfR expression in microglial cells (18). In fact, the promoter region of the TfR gene contains a hypoxia response element that mediates transcriptional activation by hypoxia-inducible factor 1 (19). The relative hypoxia-linked hyperglycemia could underlie the increased serum sTfR concentration in states of altered glucose tolerance (20).

A scenario can be envisioned in which the physiological action of insulin leads to increased uptake of different nutrients and iron. Any factor causing hyperinsulinemia (weight gain, aging, repeated usual-life infections) amplifies this process, determining increased deposition of iron, which in the long term worsens insulin resistance. Once insulin secretion declines, this regulation is lost. At this stage, uptake of excess iron is probably regulated by the reticuloendothelial system.

With the information contained in this article, it will be important to test if serum sTfR concentration is equally useful in evaluating total erythropoiesis in patients with altered glucose tolerance compared with individuals with NGT.

In summary, both insulin sensitivity and insulin secretion are significantly associated with serum sTfR concentrations, although insulin sensitivity independently predicts circulating sTfR, mainly in subjects with NGT. The implications of these interrelationships between iron and glucose metabolism should be investigated further.

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References

1. Finch C: Regulators of iron balance in humans. *Blood* 84:1697–1702, 1994
2. Davis RJ, Corvera S Czech MP: Insulin stimulates cellular iron uptake and causes the redistribution of intracellular transferrin receptors to the plasma membrane. *J Biol Chem* 261:8708–8711, 1986
3. Yokomori N, Iwasa Y, Aida K, Inoue M, Tawata M Onaya T: Transcriptional regulation of ferritin messenger ribonucleic acid levels by insulin in cultured rat glioma cells. *Endocrinology* 128:1474–1480, 1991
4. Tanner LI, Lienhard GE: Localization of transferrin receptors and insulin-like growth factor II receptors in vesicles from 3T3–L1 adipocytes that contain intracellular glucose transporters. *J Cell Biol* 108: 1537–1545, 1989
5. Quinlan GJ, Chen Y, Evans TW, Gutteridge JMC: Iron signalling regulated directly and through oxygen: implications for sepsis and the acute respiratory distress syndrome. *Clin Sci* 100:169–182, 2001
6. Baynes RD, Cook JD: Current issues in iron deficiency. *Curr Opin Hematol* 3: 145–149, 1996
7. Hernández C, Lecube A, Carrera A, Simó R: Soluble transferrin receptors and ferritin in type 2 diabetic patients. *Diabet Med* 22:97–101, 2005
8. Fernández-Real JM, López-Bermejo A, Ricart W: Cross-talk between iron metabolism and diabetes. *Diabetes* 51:2348–2354, 2002
9. Fernández-Real JM, Broch M, Richart C, Vendrell J, López-Bermejo A, Ricart W: CD14 monocyte receptor, involved in the inflammatory cascade, and insulin sensitivity. *J Clin Endocrinol Metab* 88:1780–1784, 2003
10. Gubern C, López-Bermejo A, Biarnés J, Vendrell J, Ricart W, Fernández-Real JM: Natural antibiotics and insulin sensitivity: the role of bactericidal and permeability increasing protein (BPI). *Diabetes* 55: 216–224, 2006
11. Fernandez-Real JM, Lopez-Bermejo A, Vendrell J, Ferri MJ, Recasens M, Ricart W: Burden of infection and insulin resistance in healthy middle-aged men. *Diabetes Care* 29:1058–1064, 2006
12. Gatter KC, Brown G, Trowbridge IS, Woolston RE, Mason DY: Transferrin receptors in human tissues: their distribution and possible clinical relevance. *J Clin Pathol* 36:539–545, 1983
13. Moutafchiev DA, Sirakov LM: Effect of insulin and adrenaline on the 59Fe transferrin uptake of lactating mouse mammary gland cells. *Horm Metab Res* 24:420–423, 1992
14. Clairmont KB, Czech MP: Insulin injection increases the levels of serum receptors for transferrin and insulin-like growth factor-II/mannose-6-phosphate in intact rats. *Endocrinology* 127:1568–1573, 1990
15. Tsuji Y, Miller LL, Miller SC, Torti SV, Torti FM: Tumor necrosis factor-alpha and interleukin 1-alpha regulate transferrin receptor in human diploid fibroblasts: relationship to the induction of ferritin heavy chain. *J Biol Chem* 266: 7257–7261, 1991
16. Johnson D, Bayele H, Johnston K, Tennant J, Srai SK, Sharp P: Tumour necrosis factor alpha regulates iron transport and transporter expression in human intestinal epithelial cells. *FEBS Lett* 573:195–201, 2004
17. Yki-Jarvinen H: Glucose toxicity. *Endocr Rev* 13:415–431, 1992
18. Kaur C, Ling EA: Increased expression of transferrin receptors and iron in amoeboid microglial cells in postnatal rats following an exposure to hypoxia. *Neurosci Lett* 262:183–186, 1999
19. Lok CN, Ponka P: Identification of a hypoxia response element in the transferrin receptor gene. *J Biol Chem* 274:24147–24152, 1999
20. Williamson JR, Chang K, Frangos M, Hasan KS, Ido Y, Kawamura T, Nyengaard JR, van den Enden M, Kilo C, Tilton RG: Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes* 42:801–813, 1993