



IRON AND GLUCOSE HOMEOSTASIS IN PATIENTS WITH DIABETES: CORRELATION BETWEEN sTfR AND sRAGE

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ABSTRACT

Insulin controls iron homeostasis and vice versa iron affects the action of insulin. Generally there is a reverse association with iron stores (ferritin) and iron necessity (soluble transferrin receptor- sTfR) which is not found by all authors in patients with diabetes. sTfR are a measure of erythropoiesis effectiveness and represent the needs of iron. In common population the iron stores are positively associated with the development of glucose intolerance in diabetes. The accepted as a sensitive marker for determination of metabolic control rate glycated hemoglobin (HbA1C), does not show the observed dependencies between hyperglycemia and iron homeostasis changes in diabetes. Our work hypothesis was that the abilities of the cell to express iron containing proteins (ferritin), receptors for iron containing proteins (TfR) and receptors for glycated proteins (RAGE) depend on the degree of hyperglycemia. The results obtained show that in the groups with higher values of glycated hemoglobin (HbA1C>8.5), used as a marker for hyperglycemia, the adaptive mechanisms maintaining iron homeostasis in diabetes are declined. Our results showed decreased levels of both sTfR and sRAGE (soluble receptor for advanced glycation end products) and simultaneously higher concentration of serum ferritin. The investigation of the existing associations between iron and glucose homeostasis showed that sRAGE was a sensitive marker for an upcoming iron deficiency, associated with sTfR levels (a marker for an adequate supply of iron for the cells).

Key words: diabetes, glycated hemoglobin, sTfR, sRAGE, ferritin

INTRODUCTION

Insulin controls iron homeostasis and vice versa iron affects the action of insulin (1-5). Generally there is a reverse association with iron stores (ferritin) and iron necessity (soluble transferrin receptor -sTfR) which is not found by all authors in patients with diabetes (2). Soluble transferrin receptors are a measure of erythropoiesis effectiveness and represent the needs of iron (1). In common population the iron stores are positively associated with the development of impaired glucose metabolism in diabetes (6). The accepted as a sensitive

marker for determination of metabolic control rate HbA1C, does not show the observed dependencies between hyperglycemia and iron homeostasis changes in diabetes (2). This is so because HbA1C represents retrospectively the hyperglycemia condition, since the life of the erythrocyte is 120 days. Our aim was to search for more reliable markers in diabetes which associate iron homeostasis with hyperglycemia. Such marker is the soluble receptor for advanced glycation end products – sRAGE, which serum levels represent the cells ability for adapting in hyperglycemia.

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The role of serum ferritin in pathobiochemical changes in diabetes is also not well investigated, because ferritin participates both as an iron store protein and as an acute phase protein (6, 7).

MATERIALS AND METHODS

The study involved 81 diabetics from the Clinic of Endocrinology, Medical University-Plovdiv, 46 female and 35 male, 58±15 years old with duration of diabetes 1-37 years. 7 patients were with recently discovered diabetes, 47 patients were treated with insulin and 27 patients were treated with peroral medicines and appropriate diet. Within 23 patients with diabetes, 9 treated with peroral medicines, 9 treated with insulin and 5 with recently discovered diabetes (not treated), we searched for a correlation between sRAGE and sTfR. Serum levels of sRAGE and sTfR were determined with ELISA kits (BioVendor Research and Diagnostic Products, Czech Republic), ferritin was determined with ELISA kit (Minias Globe Diagnostics Srl, Italy), the glycated hemoglobin HbA1C was determined

with Nyco Card Reader (Norway) using affinity chromatography principle and refractometric detection.

RESULTS AND DISCUSSION

Table 1 shows the mean values of the investigated parameters of iron and glucose homeostasis in patients with diabetes which are compared with the normal values according to data from literature. The mean values for ferritin, glycated hemoglobin and glucose are higher while the mean values for sRAGE are lower than normal values. The mean sTfR values do not differ from the controls. This is probably due to disturbances which do not allow an adequate expression of transferrin receptors in iron deficiency conditions because of immunoinflammatory changes in diabetes (7)

Table 1. Iron homeostasis parameters and glucose in patients with diabetes

Parameter	X±SD	Normal values
sTfR	1.013 ± 0.570 (n=79)	1-2.9 µg/mL*
sRAGE	994.87 ± 735.96 (n=80)	1525.9 ± 471.6 pg/mL*
ferritin	271.75 ± 135.02 (n=78)	Men -183 (21-385) ng/mL* Women -49 (7-187) ng/mL*
HbA1C	9.46 ± 2.19 (n=81)	< 7 %
glucose	13.29 ± 5.4 (n=80)	4.5-5.5 mmol/L
ESR	30.01 ± 18.71 (n=80)	< 30 mm/h- Women < 20-22 mm/h- Men

*The values are taken from the ELISA kits used in the research (BioVendor, Czech Republic, Minias Globe Diagnostics Srl, Italy).

The results obtained show that in the groups with higher values of glycated hemoglobin (HbA1C >8.5), used as a parameter for hyperglycemia, the adaptive mechanisms for maintaining iron homeostasis are impaired. Because of the immunoinflammatory changes in diabetes iron stores as ferritin in cells of reticuloendothelial system and the iron depletion is accepted as a protective mechanism in inflammation and infections (2). Serum ferritin represents the iron stores in human body but it is also an acute phase protein. That's why its increasing can not be explained simply. In iron deficiency the cells adaptive mechanism is the expressing of more transferrin receptors which catch traces of iron. sTfR is accepted as a serum parameter for the cells needs of iron and it represents the levels of membrane transferrin receptors expression (1). In patients with impaired glucose metabolism reliably increased levels of serum transferrin and ferritin and a negative correlation between sTfR and serum ferritin

are found (2). Other authors, however find increased serum levels of ferritin in absence of reciprocally sTfR decreasing in patients with diabetes type 2 (7).

Table 2 shows that the compensating mechanisms of functional iron deficiency in diabetes are more effective in the group of patients with diabetes with lower degree of hemoglobin glycation (HbA1C<8.5). In this group sTfR values are with 12 % higher. The deeper pathobiochemical changes in the group with HbA1C>8.5 are probably the reason for the reliably higher ferritin values (with 20 %, p<0.05) in comparison with the group with lower glycated hemoglobin (**Table 2**).

sRAGE is a soluble receptor for glycated proteins. It is a truncated form of a cellular receptor expressed on many cells (endothelial cells, macrophages, etc.) and binds glycated proteins- AGE (Advanced glycation end products). RAGE mediates signals, initiated from inflammation stimuli and participates in

pathobiochemical mechanisms of diabetes systematic complications (8). sRAGE correlates with markers of inflammation and complications in diabetes, but does not correlate with HbA1C (9).

We observed that for both sTfR and sRAGE, higher values of soluble receptors are in the group with normal and lower values of glycated hemoglobin. sRAGE values in the group with HbA1C<8.5 are with 24 %

($p<0.01$) higher (**Table 2**). Probably the cell abilities to express sRAGE decrease in response to increased hyperglycemia. Our results show a reliable positive correlation between sRAGE and sTfR values in a group of patients with diabetes ($n=23$, $y=0.0003x + 0.9135$, $r=0.378$, $p<0.05$) (**Fig. 1**). At the same level of glycated hemoglobin there is no reliable correlation between sTfR and HbA1C ($n=21$, $y=-0.0908x + 1.8519$, $r=0.050$, $p>0.1$).

Table 2. Comparison of iron homeostasis parameters and sRAGE depending on HbA1C level

Parameter	HbA1C < 8.5	HbA1C > 8.5	P	% difference
sTfR, $\mu\text{g/mL}$	1.052 ± 0.465 ($n=31$)	0.928 ± 0.374 ($n=47$)	>0.1	12
Ferritin, ng/mL	239.01 ± 120.31 ($n=33$)	298.0 ± 133.0 ($n=47$)	<0.05	20
sRAGE, pg/mL	1039.69 ± 479.30 ($n=30$)	794.54 ± 376.61 ($n=51$)	<0.01	24

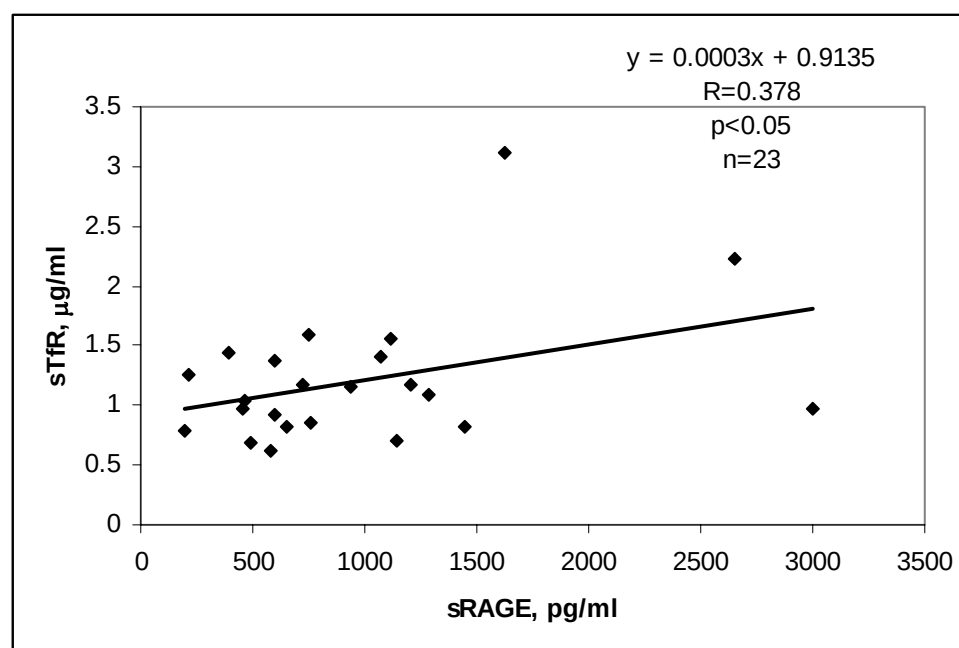


Fig. 1. Parameters of regression and correlation analysis of sRAGE and sTfR values in a group of patients with diabetes

CONCLUSIONS

1. The results obtained show that in the groups with higher values of glycated hemoglobin ($\text{HbA1C}>8.5$), used as a parameter for hyperglycemia, the adaptive mechanisms maintaining iron homeostasis in diabetes, are declined. Our results showed decreased levels of both sTfR and sRAGE and simultaneously higher concentration of serum ferritin.

2. The existing correlation between the parameters of both iron and glucose homeostasis shows that sRAGE is a sensitive parameter for an upcoming iron deficiency, which correlates with the levels of sTfR- a parameter for an adequate iron supply.

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