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DIFFERENCES OF PARAMETERS OF IRON AND GLUCOSE HOMEOSTASIS IN PATIENTS WITH DIABETES DEPENDING ON THE THERAPY, SEX AND PRESENCE OF INFLAMMATORY PROCESS

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ABSTRACT There are few and contradictory data about the association between diabetes disorders and iron homeostasis changes. The aim of the present research was to assess the significance of the therapy (with insulin or with peroral medicines), sex and presence of inflammatory process for the changes observed in the parameters of iron (sTfR and ferritin) and glucose (HbA1C and sRAGE) homeostasis in diabetes. The results obtained show that the therapy with insulin improves the adaptive abilities of the cells to express transferrin receptors and receptors for glycated proteins while at the same time decreases the pathological storage of iron in the cell stores. There are differences in the results obtained in the groups men and women with diabetes which confirms the statement in literature for a higher sensitivity of women to insulin regarding glucose metabolism, which probably results in a better control on the iron homeostasis parameters. In the group with increased ESR there are reliably higher serum levels of ferritin ($p<0.01$) and a tendency ($p>0.05$) for decreased expression of transferrin receptors, assessed from sTfR serum content.

Key words: diabetes, sTfR, sRAGE, HbA1C, ferritin, ESR, sex, therapy

INTRODUCTION

Diabetes is taking its course with immuno-inflammatory changes which impair iron homeostasis (1). The iron-transport proteins transferrin and lactoferrin supply iron in the cell stores as an adaptive mechanism, which causes increased iron stores together with hypoferemia and iron deficiency (2). The serum ferritin levels may be an useful marker for insulin resistance above a certain threshold (3, 4). In literature there are contradictory results for the association between the serum ferritin content and the concentration of soluble transferrin receptor (sTfR) which is accepted as an assessment of the normal iron content in cells (5). There are data that in patients with type 2 diabetes the serum ferritin levels increase at a lack of reciprocal decrease of sTfR (5). The authors also observe higher levels of sTfR in patients with type 2 diabetes, treated with insulin than in those, treated with peroral medicines (5). Correlation between serum concentration of sTfR and hyperglycemia rate, assessed from glycated hemoglobin, is not found (6).

It is well known that insulin regulates iron homeostasis and vice versa iron affects insulin action (7). There are also data for different metabolic effects of insulin in men and women (8). There are no evident criteria for determining whether the increased serum ferritin directly concerns the increased iron storage or it is a part of the pathobiochemical changes of the inflammatory processes in diabetes (3, 4).

The aim of our research was to assess the significance of the therapy (with insulin or

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with peroral medicines), the sex and the presence/absence of inflammatory process for the changes observed in the parameters of iron (sTfR and ferritin) and glucose (HbA1C and soluble receptor for advanced glycation end products- sRAGE) homeostasis in patients with diabetes.

MATERIALS AND METHODS

The effect of therapy is investigated in 44 patients treated with insulin and 27 patients treated with peroral medicines. The study involved 46 women and 31 men for determination of the association of sex and the changes in iron and glucose homeostasis in diabetes.

The parameters of iron homeostasis sTfR and serum ferritin are determined with ELISA kits (BioVendor Research and Diagnostic Products, Czech Republic, Minias Globe Diagnostics Srl, Italy). sRAGE are determined as cell abilities to express receptors for glycated proteins also with ELISA (BioVendor Research and Diagnostic Products, Czech Republic). The glycated hemoglobin (HbA1C) was determined with Nyco Card Reader (Norway) using affinity chromatography principle and refractometric detection.

RESULTS AND DISCUSSION

Higher values of sTfR but without statistical reliability (with 13 %, $p>0.1$) are determined in patients treated with insulin, compared with the patients treated with peroral medicines **(Table 1)**. In women there is a tendency for higher serum sTfR compared with men- 20 % ($p>0.05$) **(Table 2)**. At normal ESR there is a tendency for higher sTfR compared with the patients with increased ESR – with 16 % ($p>0.05$) **(Table 3)**.

Table 1. *Parameters for assessment of iron and glucose homeostasis in patients with diabetes depending on the therapy*

Parameters	With insulin	Without insulin	p	% difference
sTfR, μg/mL	1.073 ± 0.601 (n=44)	0.936 ± 0.536 (n=27)	>0.1	13
Ferritin, ng/mL	230.33 ± 132.33 (n=43)	315.79 ± 117.66 (n=27)	<0.01	27
sRAGE, pg/mL	972.72 ± 438.11 (n=45)	791.30 ± 371.13 (n=26)	>0.05	19
HbA1C, %	9.17 ± 1.85 (n=46)	9.23 ± 2.16 (n=27)	>0.1	0.6
ESR, mm/h	26 ± 16 (n =46)	30.0 ± 17 (n=29)	>0.1	13

Serum ferritin is with 27 % ($p<0.01$) reliably higher in patients treated without insulin **(Table 1)** and with 31 % ($p<0.001$) in men **(Table 2)**. In the group with increased ESR there is a reliably higher level of serum ferritin with 23 % ($p<0.025$) **(Table 3)**.

The HbA1C values do not depend on the type of therapy, sex and ESR **(Table 1-3)**.

There is a tendency for higher values of sRAGE (with 19 %, $p>0.05$) in patients treated with insulin **(Table 1)**. In women there is reliably higher levels of sRAGE- with 21 % ($p<0.001$) compared with men **(Table 2)**. Differences in sRAGE values depending on ESR were not found **(Table 3)**.

Table 2. *Parameters for assessment of iron and glucose homeostasis in men and women with diabetes*

Parameters	women	men	p	% difference
sTfR, μg/mL	1.105 ± 0.615 (n=46)	0.879 ± 0.489 (n=31)	>0.05	20
Ferritin, ng/mL	232.92 ± 129.47 (n=47)	335.64 ± 113.22 (n=29)	<0.001	31
sRAGE, pg/mL	955.34 ± 415.25 (n=46)	754.04 ± 371.13 (n=29)	<0.001	21
HbA1C, %	9.40 ± 1.83 (n=47)	9.57 ± 2.60 (n=31)	>0.1	2
ESR, mm/h	33 ± 19 (n =47)	23 ± 15 (n=31)	<0.01	30

Table 3. *Parameters for assessment of iron and glucose homeostasis in patients with diabetes at normal and increased ESR*

Parameters	with normal ESR	with increased ESR	p	% difference
sTfR, μg/mL	1.029 ± 0.545 (n=41)	0.869 ± 0.286 (n=39)	>0.05	16
Ferritin, ng/mL	243.31 ± 138.80 (n=39)	315.79 ± 117.66 (n=27)	<0.025	23
sRAGE, pg/mL	897.53 ± 350.0 (n=45)	791.30 ± 371.13 (n=26)	>0.05	12
HbA1C, %	8.95 ± 1.92 (n=41)	9.92 ± 2.34 (n=27)	>0.1	10
ESR, mm/h	17 ± 7 (n =40)	44 ± 16 (n=40)	<0.001	61

In literature there is evidence that insulin stimulates iron transport and uptake by the cell (7). It is proved that transferrin receptor co-localizes with insulin dependent glucose transporters on microsomal adipocyte membranes (9). Our results support these findings because in patients treated with insulin there is 13 % higher serum content of sTfR **(Table1)**. With more investigated patients an increase in the statistical reliability of the found difference could be expected. Insulin affects favourably two more of the investigated parameters: by comparison between the diabetic patients treated with insulin or with peroral medicines we found that the insulin administration improves the adaptive responses of the cell to express receptors for glycated proteins (RAGE), assessed by the soluble receptor in serum-sRAGE **(Table 1)** and also decreases the pathological iron storage as ferritin which causes iron deficiency in diabetes (3, 4) **(Table 1).**

There is evidence that women are more sensitive to insulin regarding glucose metabolism in muscles which reflects on iron homeostasis (8). This fact can probably explain the results obtained in the present study according to which in women we observed a tendency for significantly less pathological iron storage (with 31 %, $p<0.001$) **(Table 2)** and more optimum cell adaptation to iron deficiency, shown as an ability for higher expression of transferrin receptors (with 20 %, $p>0.05$), assessed by the serum content of sTfR **(Table 2)**. The higher sensitivity to insulin in women could explain also the better adaptation to hyperglycemia by expression of receptors for glycated proteins (sRAGE)- the mean values in women are reliably higher (with 21 %, $p<0.001$) in comparison with men **(Table 2).** There is experimental evidence that estrogens inhibit the oxidative stress in mitochondria isolated from brain (10). The oxidative stress induces insulin resistance by decreasing the internalization of insulin and increases ferritin synthesis (11). An indirect correcting effect of estrogens on the investigated parameters could be supposed via decreasing of the pathobiochemical disturbances caused by the oxidative stress in diabetes. A target for the antioxidant protection of estrogens is the mitochondrial enzyme aconitase which is sensitive to the action of oxygen radicals (11). It is well known that aconitase is responsible for the post translational control, mediated by iron. Aconitase dissociates from mRNA when it binds iron. The binding of aconitase to 5' UTR of mRNA for ferritin blocks the initiation of translation; the binding to 3' UTR of mRNA for transferrin receptor blocks the site for endonucleases degradation and in this way stabilizes mRNA for transferrin (12). It could be supposed an estrogen-dependent correction of the iron homeostasis disturbances at the level of post-translational control which is more expressed in women with diabetes **(Table 2).**

The accepted parameter for an assessment of present inflammatory process- ESR is not the most precise but it is an orienting one for the upcoming changes attendant inflammation. The results obtained show that in the group with increased ESR there is a reliable increase of serum ferritin (with 23 %, $p<0.05$). This fact confirms that ferritin except as iron storage protein participates in the inflammation mechanisms (1), (Table 3). There is evidence that in patients with impaired glucose metabolism increased levels of serum ferritin are found (4). The evidence for existing correlation between ferritin and sTfR are contradictory (1, 4). According to our results in patients with diabetes with increased ESR there are higher levels of ferritin and lower content of soluble transferrin receptors **(Table**

3). These results could be explained as decreased ability of the cells to react on the upcoming iron deficiency caused by its deviation in cells of reticuloendothelial system. In fact the assessment of iron deficiency for the cells is masked from the higher ferritin levels which in this case are caused by unlocking pathological mechanism of iron storage **(Table 3).**

CONCLUSION

The results obtained show differences in the parameters of iron and glucose homeostasis which could enable to associate the observed pathobiochemical changes with the therapy, sex and the presence of common inflammatory process in patients with diabetes. According to the results obtained there is an obvious association between ferritin and inflammation process and differences in the parameter according to the sex must be rendered an account. The cells keep better adaptive responses to express transferrin receptors and sRAGE in diabetic women and in the patients with normal ESR. The therapy with insulin has a better corrective effect, assessed by all of the investigated parameters, compared with the taking of peroral medicines. We observed higher sensitivity of sRAGE compared with HbA1C for an assessment of the changes observed in the iron homeostasis parameters according to the therapy (with insulin or with peroral medicines), sex and the presence/absence of inflammatory process.

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