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Relationships between adiponectin, sex hormone binding globulin and insulin resistance in hyperthyroid Graves' disease women

Powiązania pomiędzy adiponektyną, białkiem wiążącym hormony płciowe i opornością insulinową w nadczynności tarczycy u kobiet z chorobą Gravesa

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Abstract

Introduction: Adiponectin and sex hormone binding globulin (SHBG) play a role in glucose metabolism. Hyperthyroidism has an impact on carbohydrate metabolism and could affect insulin resistance. The aim of this study was to assess the associations between insulin resistance, adiponectin and SHBG among hyperthyroid Graves` disease (GD) women.

Material and methods: The study was undertaken in 60 women with hyperthyroidism in the course of GD; 32 healthy women matched by BMI and age formed the control group. The concentrations of: free thyroxine (fT4), free triiodothyronine (fT3), thyroid-stimulating hormone (TSH), SHBG, insulin, adiponectin and glucose were measured, and the homeostasis model assessment (HOMA-I) was calculated.

Results: Compared to euthyroid subjects, hyperthyroid GD women had elevated glucose, fT4, fT3, adiponectin and SHBG concentrations, but there were no differences in HOMA-I. When we explored the relations between adiponectin as well as SHBG with glucose and HOMA-I, we observed that HOMA-I was associated with adiponectin and SHBG only in the control group, and in hyperthyroidism there were no such connections. We found positive associations between adiponectin, SHBG, fT4 and fT3 in the GD group.

Conclusions: Elevated concentrations of adiponectin and SHBG were observed in hyperthyroidism but they were not related to insulin resistance. **(Endokrynol Pol 2013; 64 (1): 26–29)**

Key words: *hyperthyroidism, insulin resistance, adiponectin, SHBG*

Streszczenie

Wstęp: Adiponektyna i białko wiążące hormony płciowe (SHBG) odgrywają rolę w metabolizmie glukozy. W nadczynności tarczycy często występują zaburzenia gospodarki węglowodanowej i oporność insulinowa. Celem pracy była próba oceny powiązań pomiędzy adiponektyną, SHBG i opornością insulinową u kobiet z nadczynnością tarczycy w przebiegu choroby Gravesa.

Materiał i metody: Badanie przeprowadzono wśród 60 kobiet z nadczynnością tarczycy w przebiegu choroby Gravesa. 32 zdrowe kobiety stanowiły grupę kontrolną. Grupy nie różniły się między sobą pod względem wieku i BMI. Oceniano stężenie: wolnej tyroksyny (fT4), wolnej trijodotyroniny (fT3), TSH, SHBG, insuliny, adiponektyny i glukozy. Oporność insulinową oceniano jako wskaźnik HOMA-I.

Wyniki: Porównując z grupą kontrolną, kobiety z nadczynnością miały wyższe stężenie fT4, fT3, SHBG, adiponektyny, glukozy, natomiast nie stwierdzono różnic we wskaźniku HOMA-I. Gdy oceniano powiązania pomiędzy adiponektyną, SHBG oraz HOMA-I i glukozą, stwierdzono korelacje tylko w grupie kontrolnej, natomiast w grupie badanej te zależności nie występowały. Wykryto powiązania pomiędzy adiponektyną, SHBG, fT4 i fT3 w grupie kobiet z tyreotoksykozą.

Wnioski: W nadczynności tarczycy występują podwyższone stężenia adiponektyny i SHBG, ale nie wpływa to na rozwój oporności insulinowej. **(Endokrynol Pol 2013; 64 (1): 26–29)**

Słowa kluczowe: nadczynność tarczycy, oporność insulinowa, adiponektyna, SHBG

Introduction

Impaired fasting glucose and impaired glucose tolerance often develop in hyperthyroidism. In patients with diabetes, the progress of diabetes is usually worsening and unstable, due to a variety of mechanisms. Thyroid hormones act antagonistically to insulin, mainly within the liver level. Gluconeogenesis and glycogenolysis increase. The expression of glucose transporter 2 (GLUT-2) in the hepatocytes and the cellular glucose transport intensifies. In the digestive tract, glucose resorption increases, secondary to the intensified expression of the sodium/glucose transporter that is located on the surface of the enterocytes. At the same time, in the course of

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Table I. *Clinical and biochemical characteristics of the hyperthyroid and control groups, *p < 0.001 tested v. control group*
Tabela I. *Porównanie parametrów klinicznych i biochemicznych pomiędzy grupą z nadczynnością tarczycy i grupą kontrolną, *p < 0.001 grupa badana v. grupa kontrolna*

	Hyperthyroid group	Control group
Number	60	32
Age (years)	45.8 ± 7.7	49.2 ± 7.3
BMI [kg/m^2]	24.6 ± 2.6	24.7 ± 2.6
Glucose [mg/dL]	91.3 ± 4.6*	87.0 ± 5.6
Adiponectin [ug/mL]	20.16 ± 5.94*	14.91 ± 4.95
SHBG [nmol/L]	115.7 ± 35.9*	86.4 ± 22.5
HOMA-I	1.4 (0.9; 1.5)	1.2 [0.8; 1.6]
TSH [mIU/mL]	0.01 ± 0.02*	1.48 ± 0.85
fT4 [ng/dL]	2.53 ± 0.54*	1.13 ± 0.32
fT3 [pg/mL]	7.13 ± 3.25*	2.55 ± 1.21

Normally distributed data is given as mean SD. Skewed data is given as median plus [25;75] percentiles. The significance tests used are the Mann-Whitney test for normally distributed variables, and unpaired t test for normally distributed variables

hormone sensitive lipase (HSL) dependent lipolysis, substantial quantities of free fatty acids are released in adipose tissue, which may contribute to the development of peripheral insulin resistance [1]. Elevated homeostasis model assessment of insulin resistance index (HOMA-I) has been reported in hyperthyroidism in some [2] but not in all studies [3]. The excess of thyroid hormones significantly affects adipocyte function, mainly lipoprotein metabolism, as well as adipocytokines secretion [4, 5]. Reduced adiponectin serum level has been shown to be a sensitive indicator of insulin resistance [6, 7]. However, several researchers have described a higher concentration of adiponectin in the hyperthyroid stage compared to healthy persons [5, 8, 9]. Another marker linked to insulin resistance is the concentration of the sex hormone binding globulin (SHBG) [10]. Insulin resistance is connected to a reduced concentration of SHBG [10], but in hyperthyroidism the secretion of SHBG increases [11]. The contribution of adiponectin and SHBG in the pathogenesis of deregulations in the carbohydrate metabolism in the course of hyperthyroidism is not known.

The aim of this study was to attempt to evaluate the connections between insulin resistance and SHBG as well as adiponectin in hyperthyroidism.

Material and methods

The study was undertaken in 60 women with hyperthyroidism in the course of Graves` disease (GD); 32 healthy women formed the control group. The groups did not differ in terms of age and body mass index (BMI). GD was diagnosed on the basis of typical clinical picture, ultrasonographic image, and increased level of TSH receptor antibodies (TRAb) and thyroid peroxidase antibodies (TPO-Abs). The patients were evaluated at the time of diagnosis. The concentrations of free thyroid hormones, i.e. free thyroxine (fT4), free triiodothyronine (fT3) and thyroid-stimulating hormone (TSH) were estimated by the radioimmunology method (ZenTech S.A.). The concentrations of SHBG and insulin were measured using RIA commercial kits (DSL), adiponectin was measured by RIA (Linco Research), and glucose with the use of Roche Diagnostic reagent. The insulin resistance index assessed by the homeostasis model assessment was calculated using the formula: HOMA-I = concentration of glucose in blood serum (mg/dL)/18.1 × concentration of insulin (ulU/mL)/22.5 [12]. The study was approved by the Bioethics Committee of the Medical University of Silesia.

Results

The concentrations of free hormones were significantly higher, and the concentration of TSH lower, in hyperthyroidism than in the control group. The glucose concentration was higher in patients with GD compared to the control group, but there weren't any differences between the groups in terms of HOMA-I (Table I). In this study we observed significantly higher concentrations of adiponectin and SHBG in the hyperthyroid group compared to the control group (Table I). We showed a significant relationship between the concentration of adiponectin and fT4, as well as between adiponectin and

Table II. *Spearman`s coefficients of the relationships between biochemical parameters in the hyperthyroid group*
Tabela II. *Współczynniki korelacji R Spearmana pomiędzy ocenianymi parametrami w grupie badanej*

Adiponectin and fT4	R Spearman = 0.33, $p < 0.001$
Adiponectin and fT3	R Spearman = 0.28, $p < 0.001$
Adiponectin and SHBG	R Spearman = 0.33, $p < 0.01$
SHBG and fT4	R Spearman = 0.35, $p < 0.001$
SHBG and fT3	R Spearman = 0.30, $p < 0.001$

fT3 in the hyperthyroid group. We also found positive correlations between the concentrations of SHBG and the concentrations of fT3 and fT4 in the hyperthyroidism group (Table II). These correlations were not present in the control group.

In both the hyperthyroid and control groups, adiponectin correlated positively with SHBG concentrations. HOMA-I was connected with BMI, SHBG and adiponectin only in healthy women but not in hyperthyroid Graves patients.

Discussion

Hyperthyroidism has an impact on carbohydrate metabolism and could affect insulin resistance. The implicated mechanisms are complex and in part unclear. Hyperglycaemia results from increased carbohydrate absorption, increased gluconeogenesis, and reduced hepatic glycogen synthesis. Hyperthyroidism can also cause a decrease in tissue reactivity for physiological insulin level, which leads to glucose and lipid metabolism dysregulation. Resistance at the molecular level is due to defects of the insulin induced stimulation cascade [13]. In this study, we observed increased fasting glucose in hyperthyroid patients, but when we evaluated insulin resistance by HOMA-I, which we determined on the basis of glucose and insulin concentration, we did not found any differences between hyperthyroid women compared to a control group. However, hyperthyroidism can lead to a reduction of BMI which promotes insulin sensitivity. Therefore insulin resistance is mediated by different confusing factors.

Adipose tissue releases a number of bioactive adipokines such as adiponectin. Serum adiponectin is inversely related to the adipose mass and intensifies insulin sensitivity. Researchers have proved that low adiponectin levels determine the grade of insulin resistance independent from fat tissue mass [7]. The globulin directly corrects the insulin signal transfer and reduces the glucose concentration without influencing insulin secretion. In skeletal muscles, through AMP kinase it intensifies the expression of GLUT-4 and the glucose uptake. Under the influence of adiponectin, the activity of enzymes responsible for gluconeogenesis decreases [6].

Excess of thyroid hormones in hyperthyroidism leads to lipolysis, a reduction of fat mass, and weight loss. Since adipose tissue is reduced in hyperthyroid subjects, secretion of adiponectin could be dysregulated. Little is known about adiponectin production in hyperthyroidism and the limited information about this issue is demonstrated by different results. In human studies, the excess of thyroid hormones have been connected with similar [4, 14] or elevated serum adiponectin levels [5, 8, 9]. In the study by Hsieh et al., the treatment of thyrotoxicosis was followed by a significant decline of serum adiponectin [15]. In the present study, higher levels of adiponectin were found in hyperthyroid GD women compared to the control group and adiponectin was not correlated with HOMA-I in hyperthyroidism. This finding does not support a role of adiponectin as a factor mediated in disturbances in carbohydrate metabolism in thyrotoxicosis.

The mechanism that binds the adiponectin production in respect of the hyperfunction severity grade is not known. In our study, adiponectin concentrations correlated positively with the concentrations of free thyroid hormones, which is compatible with reports by other researchers [5, 8, 9, 15]. It is possible that elevated adiponectin levels might be a result of thyroid hormones stimulation on peroxisome proliferator activated receptor (PPAR) and sterol-regulatory-element-binding protein (SREBP) signaling [16, 17]. Adiponectin is produced by small, differentiating fat cells, and the adiponectin gene expression during the preadipocyte maturation increases by as much as 100 times. The transcription factors: SREBP-1c, CCAAT/enhancer-binding protein (C/EBP), and PPAR stimulate adiponectin gene expression [16]. The secretion also intensifies under the influence of insulin, which stimulates SREBP-1c. In hyperthyroid subjects, increased secretion of insulin has been demonstrated [1]. Glucocorticosteroids, catecholamines and inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha), are inhibiting factors [18]. PPAR gamma plays the main role in inducing the adiponectin gene, and the nuclear factor

agonists increase adiponectin blood concentration [19]. PPAR binds with the retinoid X receptor (RXR), and the formed dimer binds to DNA within the region of adiponectin gene promoter (PPRE, PPAR response element), which leads to gene activation [16].

Furthermore, in the present study, adiponectin correlated positively with SHBG. The connections were independent from BMI and thyroid function. Those relations have been seen before [20, 21], although their nature is not known. Gannage-Yares et al. suggested that adiponectin could be connected to the production of SHBG through hepatocytes [22]. SHBG is a glycoprotein coded by a gene located on chromosome 17. It is produced by hepatocytes under the control of different endocrine and metabolic factors. Oestradiol stimulates its synthesis, but insulin and testosterone inhibits it [23]. GH and somatomedin are important negative determinants of SHBG levels, and thyroid hormones have a strongly positive effect on the production of SHBG. Increased production of SHBG in hyperthyroidism has been seen previously [11], and was confirmed in our study. We also observed the positive correlations between SHBG and thyroid hormones. Selva et al. have demonstrated that thyroid hormones increase hepatic SHBG production by increasing expression of hepatocyte nuclear factor-4 alpha (HNF 4-α) [24].

Until recently, it has been believed that SHBG synthesis in the liver was directly regulated by insulinaemia. However, Selva et al. have questioned the pivotal role of insulin, and suggested that the increase of HNF 4- expression leads to higher SHBG production [25].

The important factor affected SHBG serum levels is insulin resistance. Low serum SHBG concentrations have been shown to predict the occurrence of insulin resistance in women [26]. However, in this study we did not observe relationships between SHBG concentrations and HOMA-I levels among hyperthyroid women. These observations suggest that insulin sensitivity is not mediated by SHBG in the hyperthyroid stage.

Conclusions

There are no relationships between insulin resistance, SHBG and adiponectin in hyperthyroidism. Elevated SHBG and adiponectin concentrations reflect the degree of thyroid hyperfunction.

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