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Determination of the Level of IL-6 and Vaspin in Hyperthyroid Patients Treated with Carbimazole

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Abstract

The level of adipokines (interleukin-6 and vaspin) in hyperthyroid patients treated with carbimazole drug was determined. Eighty-five male and female participated in this study, with mean age from 20-70 years. They included: negative control group of thirty euthyroid persons represented group 1, twenty-five hyperthyroid patient (positive control) included in the second group and thirty hyperthyroid patients treated with carbimazole drug for one year or less comprised the third group. By vein puncture, blood was collected, and serum was isolated and preserved at –20 C. Adipokines (interleukin-6 and vaspin) were estimated by using ELISA method. The results demonstrated that the the increase of IL-6 level was highly significant ($p<0.01$) in hyperthyroid group as compared with euthyroids. But the result showed a significant decrease in vaspin level in hyperthyroid group with treatment as compared with hyperthyroid group. However, there was a significant ($p<0.05$) decrease in the level of vaspin in hyperthyroid group with treatment in comparison to euthyroids. Also there was no significant difference in vaspin level in hyperthyroid group with treatment in comparison to hyperthyroid group. These findings suggest that the level of IL-6 increase in hyperthyroid patient and decrease after treatment with carbimazole drug for one year or less. Although vaspin level decreased in hyperthyroid patients, it decreased even after treatment with carbimazole drug for one year or less.

Keywords: IL-6, Vaspin, Hyperthyroidism, Carbimazole drug.

تعيين مستوى الانترلوكين –6 والفاسبين في مرضى فرط نشاط الغدة الدرقية المعالجين بعقار الكاربمازول

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الخلاصة

تم تعيين مستوى السايتوكينات الدهنية (إنترلوكين –6 وفاسبين) في مرضى فرط نشاط الغدة الدرقية الذين كانوا يعالجون بعقار الكاربيمازول. شارك في هذه الدراسة خمسة وثمانون من الذكور والإناث بمعدل اعمار(30–70) سنة. واشتملوا ، مجموعة السيطرة السالبة من ثلاثين شخصًا اسوياء الغدة الدرقية تمثل المجموعة الاولى ،

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وخمسة وعشرون مريضًا بفرط نشاط الغدة الدرقية (سيطرة موجبة يمثلون المجموعة الثانية وثلاثين مريضًا بفرط نشاط الغدة الدرقية كانوا يعالجون بعقار كاربيمازول لمدة عام واحد أو أقل. جمعت عينات الدم من الوريد وتم فصل الدم وخزنه في درجة حرارة −20 درجة مئوية. تم التحري عن إنترلوكين −6 وفازبين باختبار تحليل الامتصاص المناعي المرتبط انزيميا(الاليزا). أظهرت النتائج زيادة معنوية ($p \leq 0.01$) في مستوى انترلوكين−6 في مجموعة فرط نشاط الغدة الدرقية مقارنة مع اسوياء الغدة الدرقية. لكن النتيجة أظهرت انخفاضًا معنويًا في مستوى الفاسبين في مجموعة فرط نشاط الغدة الدرقية مع العلاج بالمقارنة مع اسوياء الغدة الدرقية. ومع ذلك ، كان هناك انخفاض معنوي ($p \leq 0.05$) في مستوى الفاسبين في مجموعة فرط نشاط الغدة الدرقية مع العلاج مقارنة مع اسوياء الغدة الدرقية ، كما لم يكن هناك فرق معنوي في مستوى الفاسبين في مجموعة فرط نشاط الغدة الدرقية مع العلاج مقارنة مع مجموعة فرط نشاط الغدة الدرقية. تشير هذه النتائج إلى أن مستوى الإنترلوكين 6 يزداد في مرضى فرط نشاط الغدة الدرقية وينخفض بعد العلاج بعقار الكاربمازول لمدة عام أو أقل بينما انخفض مستوى الفاسبين في مرضى فرط نشاط الغدة الدرقية ولكن مستوى الفازبين لا زال منخفض بعد العلاج بعقار الكاربيمازول لمدة عام أو أقل

Introduction:

Hyperthyroidism is a clinical syndrome characterized by hyper metabolic state due to the increased free serum thyroxine (T4) and/or free triiodothyronine (T3). It is accompanied by suppressed thyroid stimulating hormone level (TSH) levels. The most common causes of an excessive production of thyroid hormones are Graves' disease , toxic multinodular goiter and toxic adenoma [1]. Typical signs of hyperthyroidism are weight loss despite increased appetite, tachycardia, restlessness, tremor, weakness and heat intolerance [2.[

Antithyroid drugs (ATDs), radioactive iodine ablation, and surgery are the three options for treating patients with hyperthyroidism. These therapeutic options would be effective in the treatment of patients with graves' disease (GD), whereas patients with toxic multinodular goiter or toxic adenoma should have either radioactive iodine therapy or surgery [3.[

Over the past eight decades, the thionamide drugs, i.e., carbimazole and its metabolite methimazole (MMI) and propylthiouracil (PTU) have extensively been used in the management of various forms of hyperthyroidism. Carbimazole is converted to the active form, methiamazole, with similar properties to methiamazole [4].

Carbimazole is a pro antithyroid drug that belongs to thioamide group (Carbimazole, Methimazole and propylthiouracil). After being converted to its active form, MMI prevents thyroid peroxidase enzyme from iodinating and coupling the tyrosine residues on thyroglobulin. Hence, reducing the production of the thyroid hormones T3 and T4 [5].

In patients with thyroid dysfunction, changes in lipids profile and adipokines have been recorded. Thyroid dysfunction affects the lipids profile and adipokines [6]. TSH secretion could interact with cytokines released by adipocytes in euthyroid individuals [7].

Interleukin-6 (IL-6) belongs to IL-6 family which is composed of polypeptide cytokines with a four–α-helix structure and a molecular mass of 21 to 28 kDa, commonly named as B-cell stimulatory factor. It is a multifunctional cytokine produced by T cells, B cells , keratinocytes, mesangial cells, fibroblasts, several tumor cells, endothelial and monocytes cells [8]. Also it is produced by polymorphonuclear cells, eosinophils, mast cells, dendritic cells, chondrocytes, osteoblasts, monocyte/macrophages, islet cells, thyroid cells, fibroblasts, mesangial cells, adipose tissue and certain tumor cells [9].

Interleukin 6 modulates a variety of physiological events including cell proliferation, apoptosis, differentiation, and survival. among other functions, IL-6 plays roles in the immune, endocrine,

nervous and the hematopoietic systems, including inflammation, in bone metabolism and regulation of blood pressure [10].

Vaspin (visceral adipose tissue-derived serpin) is a 45.2-kDa protein that refers to a superfamily of serine protease inhibitors. It is expressed and secreted predominantly by visceral adipose tissue. It has anti-inflammatory, increased insulin sensitivity and antiatherogenic properties. Compared with other adipokines, circulating vaspin levels are low. The levels are higher in women than in men and increase with obesity [11].

In this study, the levels of two proinflammatory cytokines, IL-6 and vaspin were investigated in the serum of hyperthyroid treated patient with carbimazole drug to inspect the possible effects of this drug during treatment.

Materials and Methods

Subjects groups and samplings

The total number of participants in the study was 85 male and female individuals, with an average age from 20 to 70 years. All samples were obtained from both Al–Mustansiryah University, National Diabetes Center and Specialist Center for Deaf diseases and Diabetes glands. They were diagnosed with hyperthyroidism according to symptoms and hyperthyroidism control test score.

The study groups were as follows: -

Group 1: Thirty euthyroid healthy individuals of both sexes (5 males and 25 females) with mean age (30-70) and considered as negative control.

Group 2: Twenty-five male and female (5 males and 20 females) hyperthyroidism patients with no treatment, so it was considered as positive control.

Group 3: Thirty patients (6 male and 24 female) diagnosed with hyperthyroidism treated with carbimazole drug for one year or less.

Patients with diabetic mellitus, hypertension, autoimmune disease, kidney and liver disease were excluded from the study

Using plastic disposable syringes, about 5 ml of peripheral whole blood was aspirated from each controls and patient groups. The blood was transferred into gel tube, and in water bath, allowed to clot for ten minutes at 37C°, centrifuged at (3000 rpm) for 10 minutes. Clear serum then obtained and was stored at -20 C° until being used for adipokines parameters assay. The hemolyzed samples were discarded [12].

Interleukin-6 and Vaspin assay

IL-6 and vaspin (Bioassay Technology Laboratory, China) were measured using ELISA method. This kits were an Enzyme-Linked Immunosorbent Assay (ELISA). Human antibody against each of the two parameters was immobilized on the plate wells. Binding occurred between cytokines present in the sample and coated antibodies on the wells. As well as binding to specific cytokines in the sample occurred after addition of biotinylated human antibody. At that time Streptavidin-HRP was added and then bound to the biotinylated antibody. During the washing step and after incubation, unbound streptavidin-HRP was washed away. Color develops in proportion to the amount of human cytokines after the addition of substrate solution. The reaction was terminated by the addition of acidic stop solution and the absorbence was read at 450 nm [13, 14].

Body Mass Index

Body mass index (BMI) was calculated among all participants by dividing the weight in kilograms on the height in squared meters (kg/m^2) [15].

European Society of Human Reproduction and Embryology. Oxford Journals, Oxford University Press, 2010.

Table 1- The category of body mass index [16]

Category	BMI
Underweight	≤ 18.5
Normal	18.5-24.9
Overweight	25-29.9
Obesity	≥ 30 3

Statistical analysis

Statistical Analysis System (SAS 2012) software was used. To make a significant comparison between means, the T-test and the Least Significant Difference –LSD test (ANOVA) were used [17].

Results and Discussions

In hyperthyroidism patients, the positive correlations between some apoptosis markers and anti-TSHR antibodies, as well as between TSH and these antibodies in hyperthyroidism patients refers to an increase in the concentration of apoptosis markers, which may lead to an increase in thyroid autoantibodies levels, that affects thyroid tissue potency and increases thyroid hormone production [18].

Table 2 reveals that 6.67% from group1were underweight, 40% were normal, 33.33% were overweight and 20% were obese. Whereas 6.67% in group 2 were under weight, 46.67% were normal, 23.33% were overweight and 23.33% were obese. In addition, in group 3 3.33% were underweight, 36.67% were normal, 33.33% were overweight and 26.67% were obese

Table 2- Body mass index of studied groups.

Body mass index (BMI)	Negative control No. (%)	Positive Control No. (%)	Treatment G3 No. (%)	P-value
Under weight <0.18 kg/m^2	2 (6.67%)	2 (6.67%)	1 (3.33%)	0.0319 *
Normal 18.5 – 25 kg/m^2	12 (40%)	14 (46.67%)	11 (36.67%)	
Over weight 25.1 – 30 kg/m^2	10 (33.33%)	7 (23.33)	10 (33.33%)	
Obesity > 30 kg/m^2	6 (20%)	7 (23.33%)	8 (26.67%)	
* (P≤0.05)				

Table 3-BMI means of the studied groups.

Groups	Mean± SE BMI (kg/m^2)
Negative control	26.43 ±0.89
Positive control	24.49 ±1.16
Treatment: G3	26.98 ±0.93
LSD value	3.465 NS
P-value	0.0536

NS non-significant difference at (p≤ 0.05)

The result in Table 3 shows no-significant (p> 0.05) differences in BMI among the three groups. It measured (26.98 ±0.93, 24.49 ±1.16 and 26.43 ±0.89) in G3,G2 and G1 respectively.

Thyroid hormones, on the other hand, affect the activities of lipolytic enzymes, lipoprotein lipase, and hepatic lipase, which is one of the reasons for changes in lipid profile in hypothyroid patient. So, alteration in thyroid function correlated with BMI due to thermogenesis process. Thermogenesis increases by thyroid hormones through ATP production due to an increase in cellular activity [19].

The resting energy expenditure increases with elevated thyroid hormones especially TSH. So, the stored energy will not converted to fat, resulting in an increase in resting energy expenditure which may cause difficulties in maintaining body weight [20].

Visceral fat produce infection cytokines which have been proven to inhibit the hypothalamic-pituitary axis, leading to negative correlations between BMI and serum T4 and between BMI and serum TSH. Thermogenesis and lipolysis processes play crucial role in the adaptation process in obesity which can be affected by the changes in thyroid hormones and TSH [21].

Torlinska *et al*.,[22] demonstrated that after treatment with carbimazole, there was an increase in weight. This increasing weight was considered a simple reaccumulation of "premorbid weight" and this is consistent with our study.

Since patients with hyperthyroidism have weight loss caused by increased thermogenesis, mediated by disconnection of oxidative phosphorylation by thyroid hormones [23],. So, Carbimazole therapy can increase BMI by directly affecting thyroid hormones which have a directimapact on metabolism. Thyroid hormones cause a general rise in fat, carbohydrate and protein metabolism [24].

Table 4-IL-6 level and vaspin level means in the studied groups.

Groups	IL-6 level (ng/ L)	Vaspin level (ng/ L)
Negative control	98.11 ±9.49 b	1.809 ±0.22 a
Positive control	114.91 ±16.34 a	1.329 ±0.08 ab
Treatment: G3	82.14 ±13.92 b	1.189 ±0.22 b
LSD value	43.39 **	0.555 *
P-value	00001	0.0457
Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01).		

The result showed that there was a significant (P≤0.01) increase in IL-6 level in the positive control which measured (114.91 ±16.34 ng\L) in comparison to negative control (98.11 ±9.49 ng\L). While there was a significant (P≤0.01) decrease in the level of IL-6 in treated group 3 which measured (82.14 ±13.92 ng\L) in comparison to the positive control which measured (114.91 ±16.34 ng\L) while there was a non-significant difference in IL-6 level in group 3 (82.14 ±13.92) in comparison to the negative control group (98.11 ±9.49 ng/L), as shown in Table 4.

It was found that cytokines levels change in thyroid disease. IL-6 increased significantly before the treatment in GD patients and it decreased significantly after treatment [25].

IL-6 refers to Th2 cytokine, produced by lymphocyte which is an initial inflammatory factor, also plays an important role in humeral immune response [26]. Therefore, it affects the function of immunoreactive cells such as B lymphocytes, while stimulating the body to produce autoantibodies and accelerating the incidence of hyperthyroidism [27].

When humeral or cellular immunity is disordered, the balance of Th1 and Th2 cells is disrupted, resulting in changes in the levels of cytokines produced by them. Th2-type cytokines (like IL-6)

regulate humeral immunity by causing the body to produce a large amount of thyroid active antibodies, which promote thyroid hormone synthesis, resulting in thyroid dysfunction and hyperthyroidism [25].

IL-6 plays a critical role in vascular inflammation because it has various biological activities in different target cells. IL-6 have been found to be expressed in hypothyroid patients [28].

The level of IL-6 gradually decreased after treatment [29]. So, these suggestions reflect our result of significant increase in IL-6 in the treated group 3 after treatment with carbimazole for one year or less.

When euthyroidism was restored after carbimazole therapy, these levels returned to normal. As a result, it was hypothesized that elevated IL-6 levels in serum, may be due to increased intrathyroid IL-6 development in thyroid hyperfunction [27].

The result showed there was no significant ($P>0.05$) difference in vaspin level in positive control in comparison to the negative control. Also, there was a significant ($P\leq0.05$) decrease in vaspin level in the carbimazole treated group 3 when compared to the negative control. While no significant ($P>0.05$) difference in vaspin level in group 3 was detected as compared with the positive control. The mean of vaspin concentration in carbimazole treated group for one year or less, positive control and negative control subjects was 1.189 ±0.22 ng/L, 1.329 ±0.08 ng/L and 1.809 ±0.22 ng/L respectively (Table 4).

Thyroid hormones regulate vaspin levels. However, there have been few studies on this subject. Gonzalez *et al*. [30] discovered that vaspin mRNA levels are significantly lower in hyperthyroid rats and significantly higher in hypothyroid rats when compared to the euthyroid rats.

Also Al-Jowari [31] revealed that vaspin levels were significantly lower in hyperthyoid patients. Since thyroid disease can affect vaspin expression, the thyroid gland lesion could be linked to cytokines generated by the immune system, hence resulting in inflammatory responses.

The regulation of vaspin gene expression was studied in the rat white adipose tissue in a variety of physiological (pregnancy, nutritional status, gender and age) and pathophysiological (growth hormone deficiency gonadectomy and thyroid status) environments was linked to energy homeostasis and insulin sensitivity [32].

In contrast to euthyroid rats, vaspin mRNA levels were lower in hyperthyroid rats and higher in hypothyroid rats, according to Gonzalez *et al*. [30].

The role of adipokines, which are primarily expressed and secreted from visceral adipose tissue (like vaspin), in explaining the epidemiological relationship between visceral, fat mass and increased metabolic risk, may be a new biomarker for obesity and insulin resistance [33]. Thyroid hormones pathophysiological involvement in the regulation of vaspin and visfatin is still unknown. Changes in adipokine secretion in thyroid dysfunction could be due to adaptive mechanisms in response to the decrease or increase in basal energy expenditure and energy substrate requirements. The interactions between thyroid and cytokine networks may be influenced by cytokine network imbalances [34]. More studies are needed to clarify the relationship between vaspin and thyroid hormones.

Decreased level of vaspin after carbimazole treatment for one year or less can be explained as a result of either less duration of the treatment or low dose of this drug during treatment. Also, different patient characteristics, coexisting autoimmunity and methodological factors may explain such differences in our study results. As a result, there findings indicate that the thyroid status has a significant impact on vaspin regulation and additional research is needed to explain the role of carbimazole drug on vaspin level.

Conclusion

Decreased vaspin level after carbimazole treatment for one year or less can be explained either by the short duration of treatment or a low dose of this drug during the treatment. Furthermore, differences in our study results can be explained by differences in patient characteristics, coexisting autoimmunity and methodological factors. As a result of the findings, thyroid status has a significant impact on vaspin regulation, and more research is needed to explain the role of carbimazole drug in vaspin level alteration.

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