Original Article

The Association Zinc Alpha 2 Glycoprotein Levels with Newly Diagnosed of Thyroid Dysfunction in Iraqi Women

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Abstract

Background: A recently discovered lipolytic adipokine called zinc-α2-glycoprotein (ZAG) has been linked to the control of lipid and glucose metabolism in a variety of metabolic diseases. Studies *in vivo* and *in vitro* indicate that thyroid hormones (THs) increase the production of ZAG in hepatocytes. Yet, there is little information on how TH might interact with ZAG in a human hyperthyroidism or hypothyroidism model. This study aimed to assess the effect of THs on serum ZAG and its relation to lipid disorder in Iraqi women, who have recently been diagnosed with thyroid dysfunction. **Materials and Methods:** A case–control study was performed at the Department of Chemistry and Biochemistry/Medicine College in cooperation with National Diabetes Center/University of Mustansiriyah from January 2021 to February 2022. One hundred thirty-two samples were included in this study, all participants are women aged between 21 and 54 years, which were divided into three groups: (44) subjects serve as a control group, (44) patients with newly diagnosed hyperthyroidism, and (44) patients with newly diagnosed hypothyroidism. **Results:** The results of the current study had shown that the levels of serum ZAG elevated in the patients who have been newly diagnosed with hyperthyroidism ($P \leq 0.001$) and decreased in patients with hypothyroidism ($P \leq 0.001$) when compared with control. Patients with hyperthyroidism have low levels of cholesterol, triglycerides (TG), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL), while patients with hypothyroidism have higher levels of cholesterol, TG, HDL, and VLDL. Nonetheless, there were no significant correlations between the ZAG and TH with lipid profile in both hyperthyroidism and hypothyroidism. **Conclusion:** ZAG levels were elevated in patients with hyperthyroidism and decreased in patients with hypothyroidism. There is no correlation between the ZAG and TH with lipid profile in both hyperthyroidism and hypothyroidism.

Keywords: Adipokine, hyperthyroidism, hypothyroidism, thyroid hormone, zinc-alpha-2 glycoprotein

Introduction

Zinc-alpha-2-glycoprotein (ZAG) is a characterized adipokine synthesized and secreted mainly by adipose tissues and liver.[1] ZAG is located in different body fluids such as semen, plasma, milk, sweat, and cerebrospinal fluid.[2] ZAG is a ~41-kilo Dalton, which is a soluble protein first isolated from the plasma of humans.[3]

ZAG acts as paracrine or autocrine or both ways in adipose tissue.[1] As a lipid mobilizing factor, ZAG encourages lipolysis, prevents lipogenesis, and controls the release of other adipokines. Therefore, it is often looked on as one of the key body composition regulators, mediating obesity, and wasting.[4] The plasma concentration ZAG is affected by several factors, including health status and body weight. ZAG has been existed to have a wide range of biological activities, but the latest interest in the function of ZAG arrives from its specified lipolytic action and its possibility l role in the regulation of weight of the body.[5]

Adipokines are a class of active biological molecules secreted by adipose tissue,[6] which had been found to have a significant impact on the regulation of lipid metabolism and energy expenditure, according to a number of lines of evidence.[7]

Scientists explained that apart from abnormally circulating levels of thyroid-stimulating hormones (TSH) and thyroid

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hormones (TH), alterations in the profile of adipokines, that have been found in hyperthyroidism patients.[8] Moreover, adipocytes express high levels of TH and TSH receptors which function similar to those in thyroid, suggesting TH may participate in the regulation of adipocyte functions.[3] Thereby, thyroid dysfunction may influence the secretion of adipokines, which contributes to lipid metabolic disorders.

Hyperthyroidism, excess TH, promotes a hypermetabolic state characterized by increased resting energy expenditure, weight loss, reduced cholesterol levels, increased lipolysis, and gluconeogenesis. Conversely, hypothyroidism, reduced TH levels, is associated with hypometabolism characterized by reduced resting energy expenditure, weight gain, increased cholesterol levels, reduced lipolysis, and reduced gluconeogenesis. Therefore, TH regulates energy balance by controlling storage and energy expenditure, regulating key metabolic pathways.[9] Expression of this glycoprotein in obesity is correlated negatively with the weight of the body as well as the amount of human body fat.[10] Given that both TH and ZAG are involved in regulating energy expenditure and metabolism of lipids, moreover, *in vitro* and animal studies suggest that TH upregulates ZAG production in hepatocytes.[11] Yet, there were little studies in human of the expression of ZAG and few are known of ZAG's role in hypothyroidism, while there are no studies of ZAG's role in hypothyroidism This study aimed to assess the effect of TH on serum ZAG and its relation to lipid disorder in Iraqi women, who have recently been diagnosed with thyroid dysfunction.

Materials and Methods

Subjects

A case–control study was performed at the Department of Chemistry and Biochemistry/Medicine College/Mustansiriyah University in cooperation with National Diabetes Center/ University of Mustansiriyah from January 2021 to February 2022. One hundred thirty-two samples were collected in this work, all participants are women aged between 21 and 54 years. These samples were equally divided into three groups: (44) subjects serve as a control group, (44) patients with newly diagnosed hyperthyroidism, and (44) patients with newly diagnosed hypothyroidism. Blood samples were collected between 8:30 and 10:30 A. M after 10–12 h fasting using 10-ml disposable syringe. Blood sample was transferred into a gel tube and allowed to clot at room temperature. Then, centrifuge at 3000 rpm for 10 min for separating the serum and kept. However, a fresh sample was used for further determination of thyroid function tests (TSH, thyroxine [T4], and triiodothyronine [T3]). The rest of the serum were transported to the Eppendorf tube and stored in a deep freezer (−20°C) to be used for determination of ZAG. The current work excluded tobacco chewers, smokers, subjects with hepatic illness, renal disease, malabsorption syndrome, people with any other endocrine diseases, such as diabetes, people taking nutritional and antioxidant supplements, and people who were unwilling to give their consent.

Biochemical measurements

ZAG was measured by enzyme-linked immunosorbent assay, thyroid-stimulating hormone, thyroxine, T3, and T4 were measured by enzyme-linked fluorescent assay. Lipid profile (total cholesterol [TC], triglycerides [TG], and high-density lipoprotein [HDL]) measured by ultraviolet/ visible spectrophotometer (low-density lipoprotein [LDL] and very LDL [VLDL]) were estimated by calculation.

Statistical analyses

The statistical analyses were performed using the MedCalc@ v. 19.5 and IBM SPSS 26 programs (IBM SPSS Inc., Chicago, IL, USA). Tables and figures were presented using Microsoft Excel 2019 software. The $P \leq 0.05$ is considered statistical significance comparing the levels of ZAG among the studies groups. In the following variables, the mean ± standard deviation (SD) is shown. ANOVA was applied to discover whether there have been significant differences in various variables among the three groups.

Results

Table 1 displays the clinical and biochemical features of the study participants. The means ± SD for patients with hyperthyroidism, hypothyroidism, and control subjects were, respectively, 35.89 ± 8.12 years, 35.25 ± 8.40 years, and 35.57 ± 8.16 years. According to statistical analysis, there were no significant differences in age between these groups, proving that the patients and controls were age-matched. As demonstrated in Table 1, patients with hyperthyroidism have higher levels of ZAG (122.88 ± 10.77 ng/ml), whereas in hypothyroidism patients, ZAG has lower level (24.61 ± 5.49 ng/ml) [Figure 1].

As regards to lipid profile, hyperthyroidism patients have decrease levels of TC (132.14 ± 22.38 mg/dl), TG (89.47 ± 25.70 mg/dl),

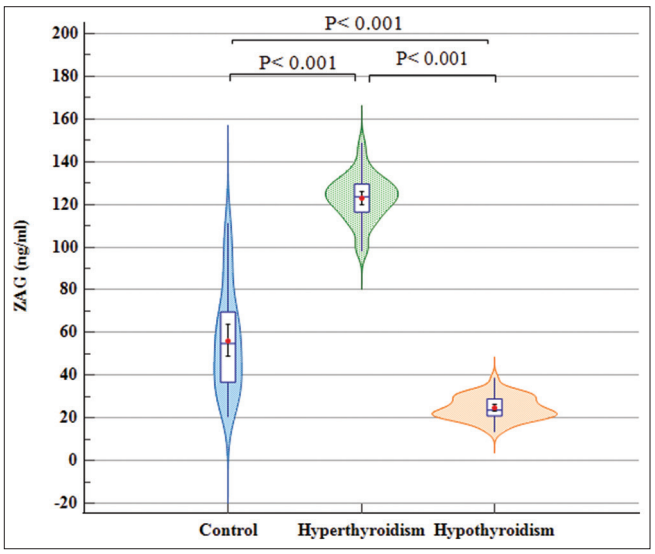

Figure 1: Violin and box plots of serum ZAG values in the control, hypothyroidism, and hyperthyroidism subjects. Red markers and the Error bars represent the means and 95% confidence intervals of the means. ZAG: Zinc-α2-glycoprotein

HDL (34.99 ± 9.10 mg/dl), LDL (71.05 ± 17.02 mg/dl), and VLDL (17.74 ± 5.15 mg/dl), whereas hypothyroidism patients have higher levels of TC (271.46 ± 18.73 mg/dl), TG (292.28 ± 42.68 mg/dl), HDL (38.83 ± 9.31 mg/dl), LDL (168.65 ± 11.39 mg/dl), and VLDL (59.88 ± 9.89 mg/dl) levels. As indicated in Table 2, there was no correlation between ZAG and THs with lipid profile in either hyperthyroidism Figures 2-4, respectively, or hypothyroidism Figures 5-7, respectively.

Discussion

Dysfunction of thyroid may affect adipokines excretion, which participates to lipid metabolic disorders. ZAG which is an adipokine distinguished that is synthesized and excreted fundamentally by adipose tissues and liver. Function of ZAG arrives from its specified lipolytic action and its possible role in controlling the weight of body weight.[12]

Results of the current study showed that hyperthyroidism patients have higher levels of ZAG compared to the control group and these results were in agreement with previous studies of Simó *et al*.,[11] who showed that increased of ZAG levels were revealed in hypothyroidism patients than control. Furthermore, the results of the current study of Xiao *et al*.[3] and study of Ali *et al*.,[13] serum ZAG levels elevated in hyperthyroidism patients, whereas in hypothyroidism patients have lower serum levels of ZAG. It is worth nothing that there were no previous studies of serum ZAG with TH in newly diagnosed hypothyroidism and this is the first study.

ZAG can preserve reverse obesity-related fatty liver by improving hepatic steatosis, insulin resistance, and inflammation and, besides enhance adipocyte browning, again mentioning its new role in the metabolism of lipids.[2]

Numerous putative underlying mechanisms have been proposed to explain these changes in lipid metabolism: (i) TH can directly trigger a series of pathways mainly involved in lipid metabolism and energy homeostasis, such as phosphoinositide 3-kinase/Akt, MAPK/extracellular signal-regulated kinases, sirtuin 1, also known as NAD-dependent deacetylase sirtuin-1, and peroxisome proliferator-activated receptors.[14] (ii) More importantly, TH participates in the regulation of adipocyte functions including secreting adipokines.[15] TH excess leads to prominent changes in classical adipokines (such as adiponectin, leptin, and resistin, suggesting that serum ZAG which is a novel lipid-mobilizing adipokine could be changed in hyperthyroidism patients.[3]

ZAG, which is encoded by AZGP1 gene, stimulates lipolysis in humans and induces a reduction in body fat in mice. Interestingly, TH increases the expression of ZAG in hepatic cells, which might also contribute to the lipolytic action of TH.[14]

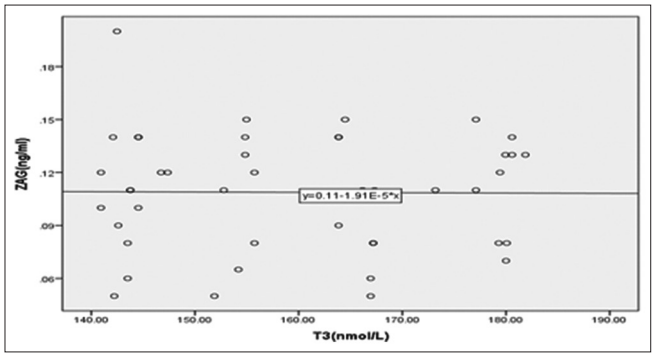

Figure 2: Correlation of serum ZAG with T3 in hyperthyroidism patients. ZAG: Zinc-α2-glycoprotein, T3: Triiodothyronine

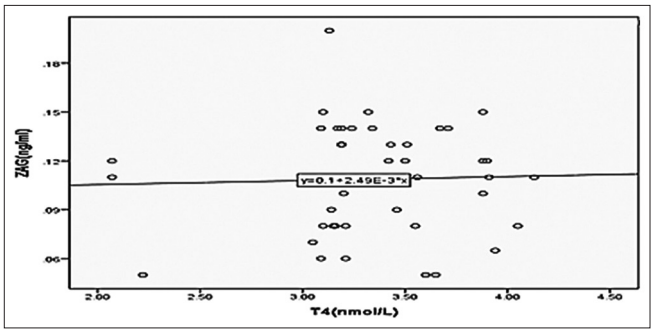

Figure 3: Correlation of serum ZAG with T4 in hyperthyroidism patients. ZAG: Zinc-α2-glycoprotein, T4: Thyroxine

Table 1: Biochemical and clinical features in study groups

Variables	Controls (*n*=44)	Hypothyroidism subjects (*n*=44)	Hyperthyroidism subjects (*n*=44)	*P* (ANOVA)
Age (years)	35±8.16	35±8.40	35±8.12	0.94
TSH (μIU/L)	2.34±0.97	10.46±1.55	0.11±0.03	<0.001**
T4 (nmol/L)	93.71±13.70	27.16±4.05	159.44±14.26	<0.001**
T3 (nmol/L)	1.53±0.35	0.23±0.06	3.34±0.45	<0.001**
ZAG (ng/mL)	56.21±24.51	24.61±5.49	122.88±10.77	<0.001**
Cholesterol (mg/dL)	159.60±27.97	271.46±18.73	132.14±22.38	<0.001**
TG (mg/dL)	133.65±26.82	292.28±42.68	89.47±25.70	<0.001**
HDL (mg/dL)	49.95±18.09	38.83±9.31	34.99±9.10	<0.001**
VLDL (mg/dL)	26.81±5.54	59.88±9.89	17.74±5.15	<0.001**
LDL (mg/dL)	91.05±19.21	168.65±11.39	71.05±17.02	<0.001**

**Significant at *P*<0.001. Results are shown as mean±SD. ZAG: Zinc-α2-glycoprotein, TG: Triglycerides, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormones, SD: Standard deviation, T3: Triiodothyronine, T4: Thyroxine

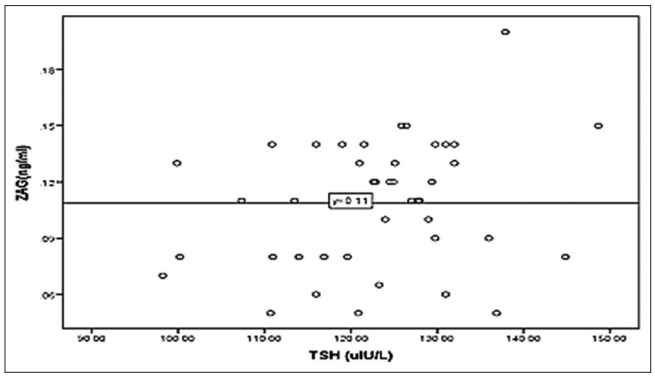

Figure 4: Correlation of serum ZAG with TSH in hyperthyroidism patients. ZAG: Zinc-α2-glycoprotein, TSH: Thyroid-stimulating hormones

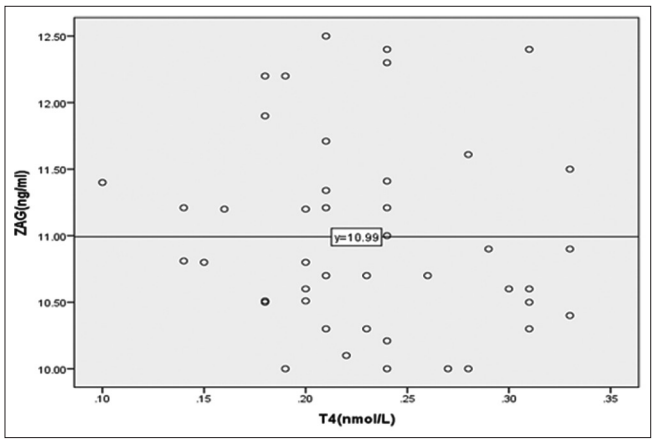

Figure 6: Correlation of serum ZAG with T4 in hypothyroidism patients. ZAG: Zinc-α2-glycoprotein, T4: Thyroxine

Table 2: Pearson correlation between the Zinc-alpha-2 glycoprotein with third hormone and lipid profile in hypothyroidism and hyperthyroidism

Parameters	Hypothyroidism (*r*, *P*)	Hyperthyroidism (*r*, *P*)
TSH (μIU/L)	0.14, 0.35	0.25, 0.18
T4 (nmol/L)	0.07, 0.64	−0.2, 0.64
T3 (nmol/L)	0.00, 1.00	−0.05, 0.74
Cholesterol (mg/dL)	0.04, 0.81	−0.12, 0.42
TG (mg/dL)	−0.02, 0.15	0.1, −0.50
HDL (mg/dL)	0.01, 0.51	−0.05, 0.75
VLDL (mg/dL)	−0.013, 0.66	−0.15, 0.33
LDL (mg/dL)	0.07, 0.42	−0.11, 0.46

ZAG: Zinc-α2-glycoprotein, TG: Triglycerides, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormones, T3: Triiodothyronine, T4: Thyroxine

Numerous studies have shown that changes in ZAG serum concentrations are strongly correlated with dyslipidemia in a variety of endocrine metabolic disorders, including type 2 diabetes mellitus, polycystic ovaries, Cushing's syndrome, growth hormone deficiency, metabolic syndrome, nonalcoholic fatty liver disease, and obesity.[16,17]

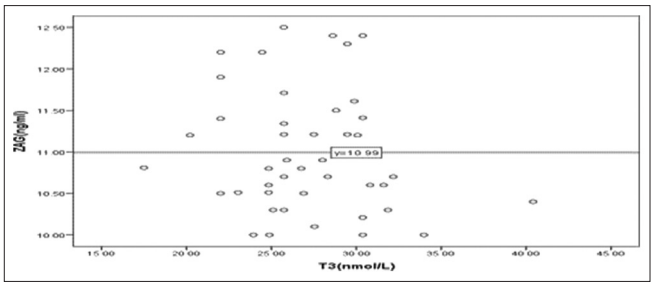

Figure 5: Correlation of serum ZAG with T3 in hypothyroidism patients. ZAG: Zinc-α2-glycoprotein, T3: Triiodothyronine

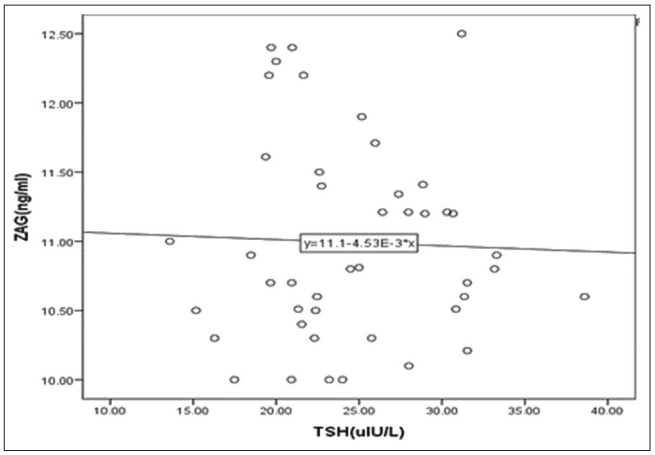

Figure 7: Correlation of serum ZAG with TSH in hypothyroidism patients. ZAG: Zinc-α2-glycoprotein, TSH: Thyroid-stimulating hormones

Regarding to lipid profile, the current study results showed that serum TC, TG, and LDL levels were significantly low in the hyperthyroidism group comparing to the group of control. These results were in agreement with the results of the study Prajitno *et al*.,[12] in which the serum of TC, TG, and LDL levels was decreased in patients with hyperthyroidism when compared to the control group, whereas in hypothyroidism, the results of the present study appeared that serum TC, TG, LDL, and VLDL significantly increased when compared to the group of control. Furthermore, the results of the current study were in agreement with previous study done by Alsalmi *et al*.,[18] who found that serum of TG, LDL-cholesterol (LDL-C), and VLDL-cholesterol levels and Kumar *et al*.,[19] who found that serum of TC and LDL-C was higher in hypothyroidism patient when compared to the group of control.

Previous study was done by Olofsson *et al*.[20] who displayed that ZAG and serum TC levels were correlated with each other both during diet-associated weight loss and healthy controls. This correlation may be due to the role ZAG plays in the body, designated in lipolysis. The scientists suggested that the correlation between ZAG and TC is the result of elevated lipolysis of TG, caused by the ZAG effects. While the results of the current study disagreement with the study above. The gene of ZAG was related with circulating blood TC levels, which may mention that ZAG plays a role in its metabolism.[4]

Conclusion

Serum ZAG levels increase in hyperthyroidism and decrease in hypothyroidism patients in the current study there is no correlation between ZAG and hormones of thyroid with lipid profile in both hyperthyroidism and hypothyroidism increasing in ZAG level which was associated with increasing in TH levels, in patients with hyperthyroidism. While decreasing in ZAG level, which is associated with a decrease in TH in patients with hypothyroidism, may probably supply clinical evidence that ZAG may be implied in the manner of development of a lipid disorder disease in hyperthyroidism patients and hypothyroidism. Further additional studies are needed to confirm our results in TH, which is associated.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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