Impact of Medical Therapy on the Zinc-A2-Glycoprotein and Ischemia Modified Albumin Levels in Patients with Hypothyroidism

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ABSTRACT

Background and objectives: Hypothyroidism is a clinical condition that needs primary care. It is increased with age and is more prevalent in females. Hypothyroidism is diagnosed biochemically, being overt primary hypothyroidism defined as serum thyroid stimulating hormone (TSH) concentrations above and thyroxin concentrations below the normal reference range.

Methods: For this purpose, 180 subjects (40 control groups and 70 patients with hypothyroidism underwent treatment for 3 months) were selected for the study. The study materials were registered from the laboratories in Kirkuk city.

Results: The results are summarized in the following points: zinc-α2-glycoprotein was highly significantly increased ($p<0.001$) in hypothyroid patients compared to the control group, according to before and after treatment. Serum Level of Ischemia Modified Albumin (IMA) was non significantly difference (0.852) in hypothyroid patients compared to the control group, according to before and after treatment. Serum Level of Human TPO (Thyroid Peroxidase) in Women was significantly difference (0.0001 significant) in hypothyroid patients compared to the control group, according to before and after treatment. The parameters of Thyroid hormones TSH, T3 and T4 were highly significantly increased ($p<0.001$) in the serum of hypothyroid patients compared to the control group, according to before and after treatment.

Conclusions: Zinc-α2-glycoprotein levels were significantly higher in patients with hypothyroidism, and no significant differences in IMA levels before and after treatment with levothyroxine in hypothyroid patients, indicating that the differences in IMA levels were due to hypothyroidism itself.

Keywords: Ischemia Modified Albumin, Zinc-α2-glycoprotein, Thyroid hormone, Thyroid Peroxidase.

INTRODUCTION

Hypothyroidism is an underactive thyroid gland. Hypothyroidism means that the thyroid gland can't make enough thyroid hormone to keep the body running normally. People are hypothyroid if they have too little thyroid hormone in the blood. Common causes are autoimmune disease, such as *Hashimoto's thyroiditis*, surgical removal of the thyroid, and radiation treatment[1].

Oral levothyroxine is primarily indicated for treating primary, secondary, and tertiary hypothyroidism. Primary hypothyroidism is when the problem occurs in the thyroid gland. Secondary hypothyroidism is when the problem is in the pituitary gland, and there is a decrease in the production of thyroid-stimulating hormone (TSH). Tertiary hypothyroidism is sporadic[2]. Additionally, levothyroxine has FDA approval for pituitary thyrotropin suppression as an adjunct to surgery and radioiodine therapy to manage thyrotropin-dependent well-differentiated thyroid cancer. This activity covers important information about prescribing levothyroxine, including mechanism of action, pharmacology, adverse event profiles, eligible patient populations, and monitoring, and highlights the interprofessional team's role in managing various forms of hypothyroidism with levothyroxine[3].

Zinc-α2-glycoprotein (ZAG), encoded by the AZGP1 gene, is a major histocompatibility complex I molecule and a lipid-mobilizing factor[4]. ZAG has been demonstrated to promote lipid metabolism and glucose utilization, and to regulate insulin sensitivity Zinc and other trace elements such as copper and selenium are required for the synthesis of thyroid hormones, and deficiency of these can result in hypothyroidism[5]. Conversely, thyroid hormones are essential for the absorption of zinc, and hence hypothyroidism can result in acquired zinc deficiency[6-7].

A novel ischemia marker named ischemia modified albumin (IMA) was previously considered as an early marker of myocardial ischemia, however due to recent reports, its contribution was demonstrated in different pathologies such as oxidative stress, diabetes, stroke, thyroid dysfunction and cancer[7]. IMA has been regarded as new and emerging marker of ischemia and oxidative stress (OXS)[8-10]. The aim of this study was to assess zinc-α2-glycoprotein and ischemia-modified albumin among patients with hypothyroidism, and to investigate the effect of Levothyroxine on zinc-α2-glycoprotein and ischemia-modified albumin levels in subjects with hypothyroidism.

MATERIALS AND METHODS

Subjects and study design: This study has investigated 180 patients with hypothyroidism (70 patients and 40 controls healthy subjects), Seventy patients newly diagnosed hypothyroidism, underwent treatment, for 3 months and complete the follow up study their ages between (20-50) years. The patients were referred to two main facilities, Kirkuk city in Azadi hospital, and Kirkuk general hospital from

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November 2023 to March 2024. Clinical history data, information on age, weight, height, marital status, menopausal status, family history of breast cancer, chronic diseases, and course of treatment were collected in a short questionnaire form. Excluded patient suffering from diabetic and chronic disease, use of oral contraceptives, antiandrogenics, glucocorticoids, and antihypertensive, antidiabetic, antiobesity drugs. smoking, hypertension.

Collection of sample: About 5 ml venous blood was collected from each case (before taken levothyroxine and 5 ml venous blood is drawn again after treatment of levothyroxine) by using a sterile disposable syringe then unloaded into gel tubes and allowed to clot at room temperature for 20 minutes. All samples were centrifuged at 3000 rpm for 10 minutes; sera removed and divided into four Eppendorf tubes 500µl for each sample, then stored at - 20 C until analysis. Serum zinc-α2-glycoprotein levels and they were measured using enzyme-linked immune sorbent assay (ELISA) kits. Thyroid function test (TSH,T_3, and T_4).

Statistical Analysis: Microsoft EXCEL 2019 and SPSS 22 were used for data entry and analysis. Descriptive statistics were presented as frequencies and were applied to explain the characteristics of participants. The comparison between the study groups was done by t-test and Chi-Square test. A P-value of less than 0.05 will be considered statistically significant.

RESULTS

The total number of a subject that participate are total 180 subjects (70 patients hypothyroidism after treatment, 70 patients hypothyroidism before treatment and 40 controls healthy subjects). This study showed that the peak age of women with hypothyroidism was between 35- 54 years and its percentage was 31%, while the least age group 15-24 years and its percentage which was found to be 29%, see (Table 1).

Table 1. Relation the number of hypothyroidism women with age

Age group(years)	No.	%
15-24	40	29%
25-34	56	40%
35-54	44	31%
Total	140	100%
Chi-Square = 4.457 p value = 0.050		

Table 2 explains the number hypothyroidism women with BMI, were 15(11%) women underweight (<18.5), 28(20%) women normal weight (18.5 – 24.9), 55 (39%) overweight (25 – 29.9), and 42 (30%) with obese (≥ 30).

Table 2. Relation the number of hypothyroidism women with BMI

BMI (Kg/m^2)		Studied group Hypothyroidism women
Underweight (<18.5)	n	15
	%	11%
Normal weight (18.5–24.9)	n	28
	%	20%
Overweight (25–29.9)	n	55
	%	39%
Obese (≥30)	n	42
	%	30%
Total	n	140
Chi-Square = 24.21, p value = 0.0007		

As shown in table (3), According to the presented data show the **mean ± SD** of the serum level of zinc-α2-glycoprotein in hypothyroidism women before and after treatment comparing with the control group (99.09 ± 27.5 versus 108.0 ± 26.7 and 143.3 ± 14.7) respectively. The result was significant (p>0.001).

Table 3. Comparison between hypothyroidism and healthy women regarding the mean ± SD of zinc-α2-glycoprotein before and after treatment

Study groups	n	zinc-α2-glycoprotein (µg/ml)	p value
Before treatment	70	99.09±27.5	P<0.001 significant
After treatment	70	108.0±26.7	
Control group	40	143.3±14.7	

As shown in (Table 4), the mean of the serum level of Human IMA in hypothyroidism before and after treatment comparing with the control group (0.422±0.122 versus 0.393±0.116 and 0.321±0.114 ng/mL) respectively. The result was non-significant (p<0.852).

Table 4. Serum Level of IMA in Women with hypothyroidism before and after treatment

Study groups hypothyroidism	n	IMA (ng/mL) Mean ± SD	P. value
Before treatment	70	0.422 ± 0.122	0.852
After treatment	70	0.393± 0.116	
Control group	40	0.321 ± 0.114	

As shown in table (5), the mean of the serum level of Human TPO (Thyroid Peroxidase) in hypothyroidism before and after treatment comparing with the control group (6171.2±506.85 versus 2966 ±1800.9 and 2829.47±279.5 pg/mL). The result was significant (P< 0.0001).

Table 5. Serum Level of Human TPO (Thyroid Peroxidase) in Women with hypothyroidism before and after treatment

Study groups hypothyroidism	n	TPO (pg/mL) Mean ± SD	t-test	p value
Before treatment	70	6171.2±506.85	0.19	P<0.0001
After treatment	70	2966 ±1800.9		
Control group	40	2829.47±279.5		

As shown in table (6), the mean of the serum level of Thyroid Hormones in hypothyroidism before and after treatment comparing with the control group, Table (7) shows that there was an increase in TSH (32.78 ±8.83 ng/ml) values before treatment of levothyroxine in cases when compared to control subjects, which is indicative of hypothyroidism and those cases were recruited for the study.

Table 6. Serum Level of thyroid tests in Women with hypothyroidism before and after treatment

Studied groups				
Hypothyroidism 140	Control group (n=40)	Before treatment (n=70)	After treatment (n=70)	p value
TSH (ng/ml)	4.48±1.68	32.78±8.83	4.26±1.77	P< 0.001
T3 (ng/ml)	5.65±2.04	1.49±0.65	6.17±1.40	P< 0.001
T4 (ng/ml)	14.86±3.11	6.85±1.72	14.83±4.21	P< 0.001

DISCUSSION

As shown in table (1) that on distributing cases according to age it was seen that most hypothyroidism cases were in aged group 25 – 34 years

of age group (i.e. 40 %), this study reveals that, the highest rate of hypothyroidism in women was within the age group 25 – 34 years and the least was within the age group of 15-24 years. Numerous results obtained by other studies were focused on the age of women with hypothyroidism, The study carried out in Iraq concluded that carried by Mohammed Habash who found that the mean age of hypothyroidism was The thyroid defects incident rate was highest in mean 31- 40 years age[11]. Almost 31.2% patients were found affected by thyroid disorders in this age group.

Earlier studies proved that age are the associated factors of thyroid defects[12]. In the survey on the diseases in the world, thyroid disorders highlighted with the highest prevalence in which 25% in females 16. Many studies have proved that prevalence of thyroid diseases found highest in female at the middle age 27-29 years age. This data is in accordance with our data where more female patients were diagnosed with the thyroid defects. This gender disparity having high prevalence in female is may be associated with estrogen and progesterone[13,14].

While the findings were observed In Yemen higher incidence of thyroid disorder was detected in female It was reported that age advances the incidence of thyroid disorders in mean age of the patient found 49 years while maximum 60 years in female. However, it was mentioned in the studies that thyroid disorder is common in older patients and having significant morbidity if not treated in early stages[15].

The results are in disagreement with Murgod and Soans *(2018)*, who found hypothyroidism is a very common symptom in women. Also found that the majority of patients were females between the ages of 31 and 45 years, the fact that women have a higher prevalence of thyroid disease, suggests that oestrogen may be involved in the pathophysiology of thyroid dysfunction. Estradiol has an antagonistic effect on the T3 and T4 hormones. The reason for this is that estradiol competes with T3 and T4 for receptor protein binding sites[16].

Obesity may play a role in thyroid dysfunction. There is evidence that low free T4 is associated with hypothyroidism[17,18]. Jia *et al* (2021) reported significant correlation between BMI and TSH in healthy adults and BMI was negatively associated with serum fT4 but had no association with serum fT3[19].

There is a positive association between TSH and obesity (BMI) which is similar to the result shown in Chinese study[20] where they explain these result as an alterations in thyroid hormones activity or as a result of an alteration in the regulation of the hypothalamic-pituitary-thyroid axis, and our results agreed with a study conducted in Iraq 2021[21].

Another study performed by *Song et al.* (2019) mentioned a strong influence of obesity on thyroid function. The authors have reported that obesity increases the risk of hypothyroidism based on meta-analysis according to previous studies[22].

González-Mereles *et al.* (2021) have examined the relationship between thyroid function and obesity. The workers have indicated a strong relationship between hypothyroidism and obesity, in which most of the hypothyroidism patients were obese[23]. Ateş *et al.* (2015), have reported a significant increase in the BMI in hypothyroidism patients compared to people with normal thyroid function. Additionally, they have reported a higher percentage of obese individuals in the hypothyroidism group compared to the control group of their study, which was our study results agreed with the previous study[24].

Dysfunction of thyroid may affect adipokines excretion, which participates to lipid metabolic disorders. ZAG 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[25].

The present study results were in disagreement with previous studies of Simó *et al*.,[26] who showed that increased of ZAG levels were revealed in hypothyroidism patients before treatments than control. Furthermore, agreement with the results of the study of Xiao et al.[27] and study of Ali et al.,[28] that serum ZAG levels in hypothyroidism patients have lower serum levels of ZAG before treatments compared with control . 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[29].

In our study, when we evaluate people who are exposed to thyroid problems compared with healthy people, a significant positive correlation was observed between the levels of zinc in the blood and T3 and T4 in the hypothyroid group , Moreover, there were critical differences in mean serum zinc levels between the groups before and after treatment of levothyroxine, as it was found that the mean serum zinc level in hypothyroid patients before taken levothyroxine was lower than in hypothyroid patients after taken levothyroxine and healthy participants. When comparing the prevalence of zinc deficiency among the current study groups, a similar pattern was observed. The current findings are consistent with those of a previous study AL-abdulaziz *et al*. [30], which indicated that in zinc deficiency patients, T3 and T4 were both lower, but TSH was essentially higher. In addition, the data of the current study showed that the level of zinc showed a negative relationship with hypothyroidism patients. However, the current study demonstrates a significant decrease in serum zinc levels in hypothyroidism.

Some previous studies Ruiz-Núñez *et al* and Kouidhi *et al*. explained most likely explanation is that albumin is the main transporter of zinc in plasma[31,32]. It was also suggested that the low level of (S) Zn in hypothyroidism could be due to sequestration of metallothionein in the liver. There was a high positive relationship between the levels of zinc in the blood of people with hypothyroidism.

Aziz *et al*. (2016) and many studies in Iraq have indicated that dietary zinc deficiency is widespread among our population[33], especially in women of childbearing age[30]. The lack of correlations between thyroid hormones with zinc levels in the blood of patients with hypothyroidism is somewhat like the results of other researchers[30] but in contrast to others[34,35]. This difference in our results compared to other studies may be molecularly related to zinc nutritional status. However, the results of our study confirmed that zinc deficiency might have an important role in thyroid function[36].

As we found a non-significant different between-study groups, the random-effects model was applied to compute the pooled effect size. Using all available data to compare serum IMA levels of hypothyroid patients compared with controls, there was a non-significant difference between these two groups in comparison with controls, the serum IMA levels were increased in hypothyroid patients before treatment of levothyroxine compared with controls and after treatment of levothyroxine with statistically non-significant p values (0.852).

Similar findings were reported in previous studies Reddy *et al.* there was no significant difference observed between before and after treatment IMA values in hypothyroid patients. The calculated was (P=0.30)[37].

This is the first time that a meta-analysis examines IMA in human with hypothyroid disease. This meta-analysis suggested that IMA levels in serum were higher in human with hypothyroid disease than healthy controls, which indicated an increased OXS status. Although the precise mechanism of IMA formation is unclear, processes such as ischaemia, hypoxia, acidosis, membrane disruption, exposure to free iron, copper and free radicals have been proposed to be involved in the formation of IMA[37].

Thyroid hormones are known to regulate mitochondrial respiration and oxidative metabolism, thus may play an important role in the regulation of free radical production and OXS[38]. Therefore, any variations in thyroid hormone status may result in a possible alteration of OXS status. While there are contrary reports in the literature on the status of OXS in with hypothyroid disease[39], hypothyroid patients are prone to increased free radical generation and OXS due to increased thyroid hormones, accelerated basal metabolic rate and oxidative metabolism[40].

In Sahithya, (2017) study the IMA values were increased in cases when compared to controls. This increased IMA value may be because of increased oxidative stress. This oxidative stress may be due to imbalance between production of oxidants and their elimination by antioxidant system in the body[41]. Our observations are in concordance with other studies done by Choudary *et al*.[42] and Ma SG *et al.*[43], therefore, IMA is found to be very useful for the detection of oxidative stress in hypothyroidism disorder.

CONCLUSION

Zinc-α2-glycoprotein were elevated significantly in hypothyroidism patients. Hence, zinc-α2-glycoprotein may be involved in the pathophysiology of hypothyroidism. 2- The differences in IMA were non-significant in the comparison between before and after treatment of levothyroxine in hypothyroid patients. This indicates that IMA differences were attributed to hypothyroidism.

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