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THE LEVELS OF CORTISOL, INSULIN, GLUCOSE AND HBA1C IN OVERT HYPOTHYROID IRAQI PATIENTS

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ABSTRACT

The present study aimed to investigate the cortisol and insulin levels and their relationship with increasing level of TSH in the overt hypothyroid male patients. The study was carried on 48 subjects in the Specialist Center of Endocrine and Diabetic Diseases in Baghdad province at Rusafa region, near AL-Kindey Hospital.The study began on10/10/2014to14/2/2015.The subjects were divided into 2 groups (control and hypothyroid).Each group included 24 males,their ages ranged between20-60years.The results showed a significant($P< 0.01$) increase in the level of TSH in overt hypothyroid patients (41.74± 3.61mu/l) in comparison with control (1.97 ± 0.264mu/l).Levels of T4nmol/L (48.59 ± 0.98) showed a significant ($p<0.01$) decrease in comparison with control (80.12±3.09). T3nmol/L (1.31±0.14); (1.52±0.083) levels showed not significantly ($p\geq0.05$) between two groups respectively.Cortisol levels (274.08 ± 9.37) ng/ml increased significantly($P<0.01$) in the patients group in comparison with control group(174.33±13.55).Insulin (15.13±1.14) µIU/ml increased significantly($P<0.01$) in the patients group in comparison with control (8.28 ± 0.76.Glucose levels mmol/l in patients (4.84±0.15) and control group(4.98±0.11)were not significant($p\geq0.05$).HbA1c(%) levels in the study group (5.50±0.18;5.50±0.18) were not significant ($p\geq0.05$)respectively.We cocluded from this study that that increasing levels of TSH causing an elevation of cortisol levels among overt hypothyroid patients with increasing insulin levels that too much cortisol in the system can induce a conversion of T4 to an improper form of T3 called reverse T3 (rT3)and any increased endogenous secretion of cortisol, altered thyroid hormone metabolism that overt hypothyroidism causes elevated cortisol levels, presumably due to both decreased clearance and blunted negative feedback of cortisol on the hypothalamic pituitary-adrenal axis(HPA).

KEY WORDS: Thyroid gland, overt hypothyroidism, cortisol, insulin.

INTRODUCTION

Thyroid is a large endocrine gland located in the neck, attached to the trachea just below the larynx. It contains two lobes connected anteriorly by a medial mass of thyroid tissue called the isthmus. The thyroid is weighing between 20 and 25 grams.[1] Hypothyroidism is defined by a decrease in thyroid hormone production and thyroid gland function.[2] Subclinical hypothyroidism is the term used to define a state in which serum T4 and T3 levels are within normal limits that evidenced by a mild increase in serum TSH. Primary hypothyroidism is overt when the serum TSH level is high and the serum total thyroxine (T4) or free T4 level is less than the population reference range.[3] Subclinical hypothyroidism is a milder degree of thyroid failure characterized by mildly to moderately increased levels of serum TSH but with total T4 and free T4 values still within the population range. The prevalence of overt hypothyroidism is approximately 1% to 2% in women and 0.1% in men[4,5], whereas subclinical hypothyroidism has been identified in 4% to 10% of different population groups[4, 5] and in up to 18% of elderly persons.[4.5,6] Progression from subclinical to overt hypothyroidism occurs in 5% to 18% of persons with subclinical hypothyroidism per year. In human studies, high cortisol has been shown to contribute to insulin resistance[7] and is likely involved in the development of type 2 diabetes, as well as the persistence of high glucose levels.[8] Cortisol is a glucocorticoid hormone produced by the adrenal cortex that is involved in the regulation of mineralocorticoids, blood pressure, immune function and metabolism.[9] Conditions that involve excess cortisol are hypertension, hypercholesterolemia, central obesity, and glucose intolerance.[10] In fact, one of the likely methods by which cortisol contributes to these diseases is by inducing a state of insulin resistance.[11] As the primary glucocorticoid released during stress, cortisol has a variety of actions: 1) impairs insulin-dependent glucose uptake in the periphery, 2) enhances gluconeogenesis in the liver, and 3) inhibits insulin secretion from pancreatic b-islet cells.All of these actions contribute to elevated glucose levels.Dysregulated cortisol levels have been shown in persons with insulin resistance, prediabetes, and type 2 diabetes.[7,8,12] Prediabetes is characterized by a fasting plasma glucose between 100-126 mg/dL. This is also known as Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT).Beyond 126 mg/dL is diagnostic of type 2 diabetes.[13] Cortisol normally follows a circadian pattern of secretion,peaking 30 minutes after waking followed by a gradual decreasethroughout the rest of the day.[14,15] In virtually any type of situation characterized by increased endogenous secretion of cortisol, a

predictable pattern of altered thyroid hormone metabolism occurs.It has long been known that frank hypothyroidism causes elevated cortisol levels, presumably due to both decreased clearance and blunted negative feedback of cortisol on the hypothalamic pituitary-adrenal axis.[16] Adrenal function is critical in the conversion of T4 to T3, which is 10 times more active than T4, in peripheral tissues. This conversion of T4 to T3 is influenced by adrenal cortisol, iron, selenium, B12 and magnesium.Too much cortisol in the system can induce a conversion of T4 to an improper form of T3 called reverse T3 (rT3).[17] [18] reported a positive relationship exists between TSH and cortisol that is maintained down to a TSH level of2.5MIU/L (but not below). Chronic elevations in serum cortisol and hypothyroidism (including subclinical hypothyroidism) have been separately linked with increased rates of depression, anxiety, and poor cognitive functioning.[19] Thus, the association between TSH levels and cortisol suggests at least the possibility of a novel pathway through which hypothyroidism (both clinical and subclinical) may promote poor mental health; Serum T3 and T4 concentrations were decreased significantly ($p < 0.05$) in geriatric study subjects as compared to controls.[20] All these effects probably result from the overall increase in cellular metabolic enzymes caused by thyroid hormone[21]

Aims of the study among hypothyroid males patients:

1-Measurment of thyroid hormones (TSH,T3,T4) levels.

2-Estimation of morning cortisol,insulin,fasting blood glucose & glycatedHbAIC.

MATERIALS AND METHODS

The study was carried out on (24) Iraqi males hypothyroid patients from Baghdad province at Specialist Center for Endocrine and Diabetic diseases and apparently healthy control subjects with total number of (24) were included in this study and they were diagnosed according to the level of of TSH, T3 and T4.The study included two groups:First group patients group(24)subjects,their age ranged between 20-60 with mean(39.00 ± 1.92). The second control group (24) subjects, aged 20-56 with mean(35.54 ± 2.29).The clinical examination was performed under supervision of physician specialist in diabetes and endocrinology. Fasting blood samples (10ml) were collected from patients and control group. The sera were separated by centrifugation at 1500 rpm for (5) min, then divided into small aliquots and kept in a deep freezer (-20º C) to be used for biochemical analysis.

Measurement of Thyroid Hormone Levels (TSH,T4,T3)

Thyroid Hormone Levels (TSH,T4,T3) were estimated in the serum,by using vidas method which is an enzyme immunoassay and Enzyme linked fluorescence assay;ELFA with Biomerieux kits. All assay steps were performed automatically by the Vidas instrument. Normal values:-TSH: 0.25-5 mu/l,**T4: 60**-120 nmol/l,**T3:** 0.4-2.3 nmol/l.

Blood glucose measurement:-Blood glucose was estimated using an Enzymatic colorimetric method according to the kits Vitro scient. Normal value:- 3.6-6.1mmol/l ;70-110mg/dl.

Measurement of Glycosylated Hemoglobin: Glycosylated hemoglobin(GHb) has been defined operationally as the fast fraction hemoglobins HbA1 (Hb A1a, A1b, A1c) which elute first during columnchromatography.[22] The non-glycosylated hemoglobin,which consists of the bulk of hemoglobin has been designated HbAo.[23;24] Normal values :4.8-5.9% HbAIc.

Measurement of insulin hormone: Insulin was measured by the electro chemiluminescence Immunoassay (ECLIA)is intended for use on Elecsys and Cobas e immunoassay analyzers. The analyzer automatically calculate the aneylate concentration of each sample either in µu/ml or pmol/l.Normal value:- 2.6-24.9 µu/ml.**Cortisol estimation:** The determination of cortisol is used for the recognition and treatment of functional disorders of the adrenal gland according to the electro chemiluminescence immune assay (ECLIA) is intended for use on Elecsys and Cobas e immunoassay analyzers. Normal values :- Am 54.9-287.6 ng/ml, Pm 24.6-171.5 ng/ml.

Statistical Analysis: The Statistical Analysis System- SAS[25] was used to effect of group (patients and control) in study parameters. Least significant difference –LSD test was used to significant compare between means in this study.

RESULTS

Table (1) shows the levels of thyroid hormones(Mean ± SE) TSHmµ/l, T4,T3noml/l in the study groups.

Table 1.Compare between patients & control in TSH,T4 andT3.

Groups	No.	Mean ± SE		
		TSH (mµ/L)	T4 (nmol/L)	T3 (nmol/L)
Patients	24	43.74 ± 3.61	48.59 ± 0.98	1.31 ± 0.14
Control	24	1.97 ± 0.264	80.12 ± 3.09	1.52 ± 0.083
LSD value	---	7.304 **	15.372 **	0.331 NS
P-value	---	0.0001	0.0002	0221
** (P<0.01), NS: Non-significant.				

The TSH level (43.74 ± 3.61) mμ/L in the patients group increased significantly (P<0.01) in comparison with controlgroup(1.97±0.264); Figure1.T4(48.59 ± 0.98) decreased significantly(P<0.01) in the patients group in comparison with control group(80.12 ± 3.09); Figure2.T3 levels showed not significantly (p≥0.05) between two groups(1.31±0.14); (1.52±0.083) respectively.

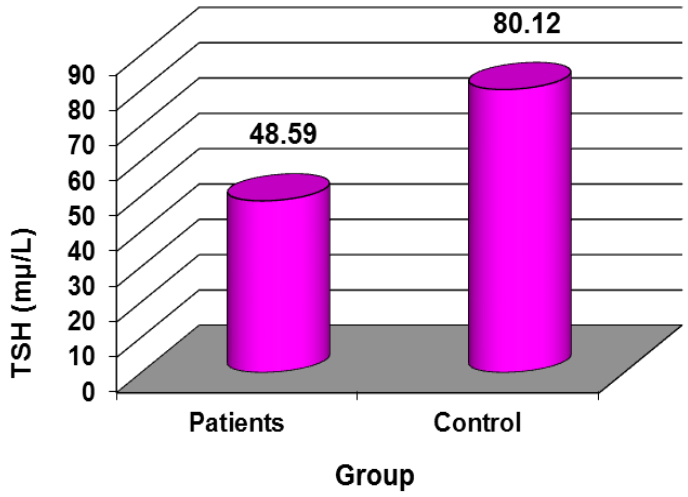

Figure 1. Compare between patients & control in TSH

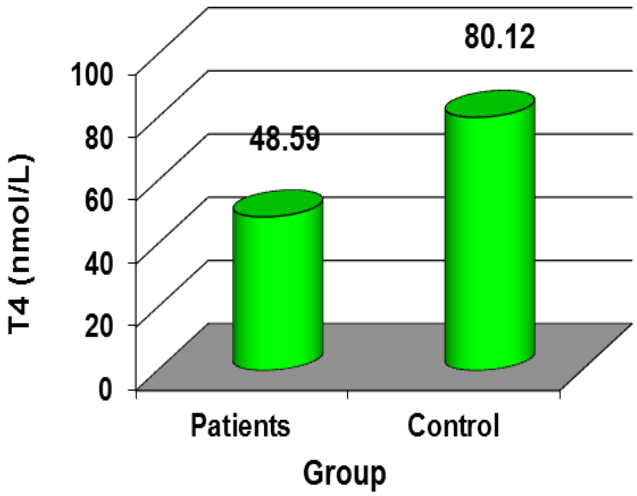

Figure 2. Compare between patients & control in T4

Table(2)shows the levels of cortisol, insulin, glucose and HbA1c% in the study groups.

Table 2: Compare between patients & control in cortisol, insulin, glucose and HbA1c%.

Groups	No.	Mean ±SE			
		Cortisol (ng/ml)	Insulin (μU/ml)	Glucose (mmol/L)	HbA1c (%)
Patients	24	274.08 ± 9.37	15.13 ± 1.14	4.84 ± 0.15	5.50 ± 0.18
Control	24	174.33 ± 13.55	8.28 ± 0.76	4.98 ± 0.11	5.54 ± 0.18

LSD value	---	33.171 **	2.753 **	0.372 NS	0.512 NS
P-value	---	0.0001	0.0001	0.461	0.871
** (P<0.01), NS: Non-significant.					

Cortisol levels (274.08 ± 9.37) ng/ml increased significantly(P<0.01) in the patients group in comparison with control group(174.33± 13.55),Figure,3.Insulin(15.13±1.14)µU/mlincreased significantly(P<0.01) in the patients group in comparison with control (8.28 ± 0.76);Figure,4.Glucose levels mmol/l in patients (4.84 ± 0.15) and control group(4.98±0.11)were not significant(p≥0.05). HbA1c (%) levels in the study groups(5.50±0.18;5.50±0.18) were not significant(p≥0.05) respectively.

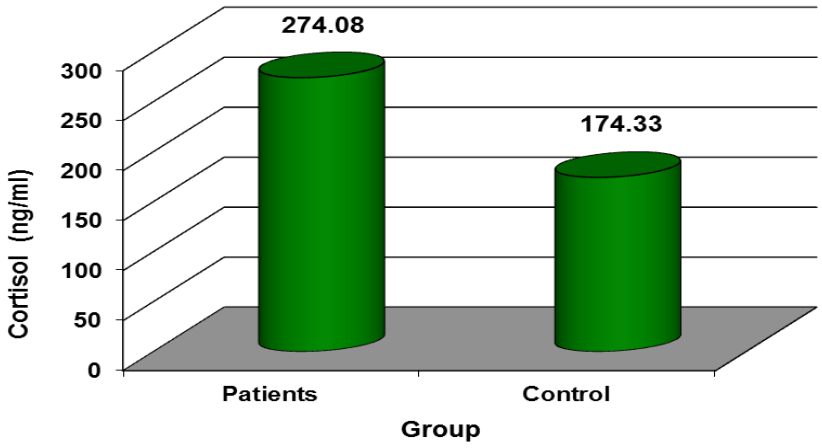

Figure 3. Compare between patients & control in Cortisol

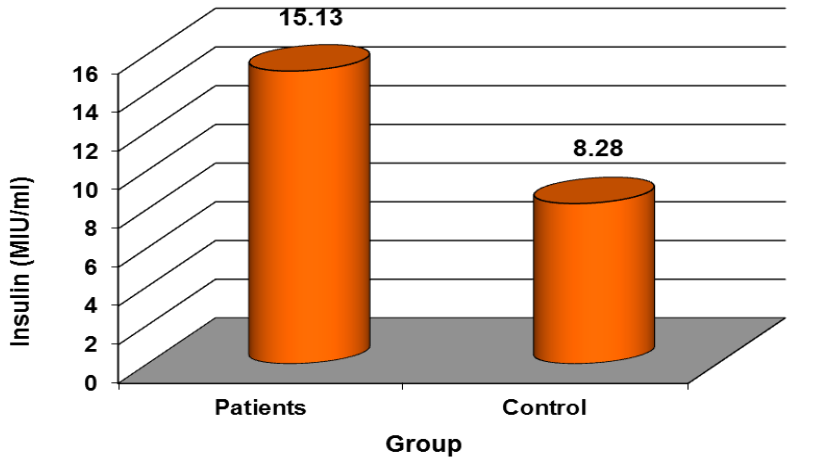

Figure 4. Compare between patients & control in Insulin

Table 3. Correlation coefficient between cortisol,insulin ,TSH

Parameters	Correlation coefficient (r)	Level of sig.
Cortisol & TSH	0.65	**
Cortisol &insulin	0.42	**
TSH&insulin	0.36	**
* (P<0.05), ** (P<0.01), NS: Non-significant.		

DISCUSSION

The increase in the level of TSH in our study table(1) reflects that thyroid function is too low,the pituitary increases its output of TSH.[26] The subclinical hypothyroidism describes a situation in which thyroid function is only mildy low,so thyroxine and T3 remains within normal range with elevated TSH level.[27] Overt hypothyroid patients in our results; that characterized by elevation of TSH level while thyroxine actually below normal values were in agreement with that reported by [3;5; 26].Our results in table(2) showed an elevation of cortisol level in hypothyroid patients group was in agreement with that reported by [16] that overt hypothyroidism causes elevation of cortisol by reducing peripheral disposal and blunting feedback of cortisol on the hypothalamic –pitutary–axis.Another potential explanation as positive relationship (0.65) between TSH&cortisol was found in our study,table3.That subclinical or clinical hypothyroidism is associated with subtle metabolic stress which could be imposing an effect on the Adrenocorticotropic hormone(ACTH) –adrenal axis leading to an increase in release and production of stress hormone (cortisol).[18] Insulin increased in patients group as[28] recorded that hyperinsulinemia observed in short-term dexamethasone-induced or corticosterone-treated rats may result from an up-regulationin glucose transporter 2(GLUT2) receptor expression which in turn stimulates glucose-stimulated insulin secretion (GSIS).However, some in vivo analysis suggest an increase in (GSIS) is a direct result of increased insulin resistance from peripheral tissues that drive insulin secretion.As[29] reported an elevated of insulin level in patients with diabetes or abdominal obesity which belong to hyperactivity of the hypothalamus-pitutary-adrenal axis is frequently found in hyper insulinemic subjects with increased plasma ACTH levels; as we have such positive correlation(0.42) between insulin and cortisol in the patients group table 3.[30] reported in primary hypothyroidism patients that glucose uptake in muscle and adipose tissue is resistant to insulin; resulting in higher levels of insulin. some studies have shown that even a subtle increase in plasma TSH levels within the physiological range may affect insulin secretion[31] and may be associated with insulin resistance and metabolic syndrome[32] as we have positive correlation(0.36)between TSH and insulin table 3.The levels of blood glucose and HbAIc% were within normal values as the hypothyroid patients in our study were non-diabetic.That HbA1c% reflects average plasma glucose over the previous 8 - 12 weeks.[33;34] While[35] reported 20 prediabetes and 38 diabetes in 58 subclinical hypothyroidism and the conclusion of this study the correlation between HbAIc was positive and significant.[36] recorded elevated HbAIC in 782 non diabetic hypothyroid.

CONCLUSIONS

We concluded from our present study that the hypothyroid patients had affected hrough.

1-Increasing levels of cortisol and its correlation with increasing TSH.

2-Increasing cortisol and its correlation with elevation of insulin levels.

3-The positive correlation between TSH, insulin; cortisol.

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