

CORRELATION BETWEEN CORTISOL; GLUCOSE LEVELS, INSULIN RESISTANCE AND BODY MASS INDEX IN OVERT HYPOTHYROID NON-DIABETIC MEN PATIENTS

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SUMMARY

The present study was conducted on 24 hypothyroid non -diabetic men patients group aged 20-60 years and 24 control group aged 20-56 years in Baghdad province at the specialist center of Endocrine and Diabetic diseases to evaluate the relationship between cortisol, insulin, glucose, glycated haemoglobin, insulin resistance, body mass index (BMI) and their correlations among non–diabetic overt hypothyroid men patients. The results in hypothyroid patients group showed highly significant ($P < 0.01$) increase in the level of TSH ($43.74 \pm 3.61 \mu\text{g/L}$); while T4 level ($48.59 \pm 0.98 \text{ nmol/L}$) decrease significantly ($P < 0.01$). T3 nmol/l levels (1.31 ± 0.14) in hypothyroid group were not significant ($p \geq 0.05$)

in comparsion with control group (1.52 ± 0.083). Cortisol ($274.08 \pm 9.37 \text{ ng/ml}$); insulin ($15.13 \pm 1.14 \mu\text{U/ml}$) increased highly significant in patients group. Fasting blood glucose (F.B.G) and HbA1C% had shown non differences. Insulin resistance and BMI increased highly significant in patients group. The results in patients group showed the following correlations; cortisol had positive correlation (0.65) with TSH and negative correlation (-0.32) with T4. Insulin resistance showed positive correlation with FBG (0.32) and BMI (0.33). BMI showed positive (0.39) correlation with increasing TSH level and negative correlation with T4 (-0.36) and no correlation with T3. We concluded from our present study that such an increase in level of cortisol in the non-diabetic overt hypothyroid men patients with increasing TSH levels had contribute to elevate insulin level with increasing insulin resistance that Insulin resistance associated with distribution of body fat subsequently leading to an increase of body mass index (BMI) among hypothyroid patients through most the positive correlations.

KEYWORDS: glycated haemoglobin, Endocrine, Diabetic and TSH.

INTRODUCTION

Cortisol is a glucocorticoid hormone produced by the adrenal cortex that is involved in the regulation of mineralocorticoids, blood pressure, immune function and metabolism.^[1] Conditions that involve excess cortisol are hypertension, hypercholesterolemia, central obesity, and glucose intolerance.^[2] In fact, one of the likely methods by which cortisol contributes to these diseases is by inducing a state of insulin resistance.^[3] 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. Dysregulated cortisol levels have been shown in persons with insulin resistance, prediabetes, and type 2 diabetes.^[4,5,6] Cortisol secretion is a major component of the stress response,^[7] and it has been implicated as a potential mediator for increased energy intake in healthy males.^[8] and females,^[9] Although acute elevation of cortisol plays a protective role during stress, chronic elevation can promote insulin resistance and abdominal obesity.^[10,11] A large waist to hip ratio (WHR), reflective of central obesity, is associated with increased vulnerability to stress.^[12,13] The association between thyroid insufficiency and depression was recognized over a century ago with an evidence of a significant relationship of compelling,^[14] The rate of hypothyroidism among the intractably depressed exceeds 50%,^[15] and some studies have found rates of depression as high as 100% among the severely hypothyroid.^[16] Subclinical thyroid insufficiency has been found in depressives at frequencies four times that of normal populations.^[17] The use of thyroid hormones to treat depression dates back at least 50 years,^[18] and reports describing resolution of depression following thyroid hormones treatment have been supported by studies.^[19] The prevalence of overt hypothyroidism is approximately 1% to 2% in women and 0.1% in men, whereas subclinical hypothyroidism has been identified in 4% to 10% of different population groups and in up to 18% of elderly persons.^[20,21] Progression of subclinical to overt hypothyroidism occurs in 5% to 18% of persons with subclinical hypothyroidism per year.^[22] In human studies, high cortisol has been shown to contribute to insulin resistance.^[23] and is likely involved in the development of type 2 diabetes, as well as the persistence of high glucose levels.^[24,25]

Aims of the study

To evaluate the correlation between cortisol levels ;Fasting blood glucose;HbA1c, insulin level;insulin resistance and body mass index (BMI)among hypothyroid non-diabetic men patients.

MATERIALS AND METHODS

The study was carried out on (24) non-diabetic Iraqi men hypothyroid patients their age ranged between 20-60 years with mean (39.00 ± 1.92) and apparently healthy control (24) subjects aged 20-56 years with mean (35.54 ± 2.29). The clinical examination was performed under supervision of specialist physicians at Specialist Center for Endocrine and Diabetic diseases in Baghdad province. Fasting blood samples (10ml) were collected from patients and control group. The sera were separated by centrifugation at 1500 rpm for (15) min, then divided into small aliquots and kept in a deep freezer (-20°C) to be used for biochemical analysis.

Measurement of Thyroid Hormone (T4,T3) & TSH levels

Thyroid Hormones (T4,T3) & TSH levels 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:- 3.9-6.1mmol/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 column chromatography. The non-glycosylated hemoglobin, which consists of the bulk of hemoglobin has been designated HbAo.

Principle

The HbA1c determination is based on the turbid dimetric inhibition immunoassay (TINIA) for hemolyzed whole blood in the Cobas c111 system .The method uses Tetra decyltrimethyl ammonium bromide (TTAB)as the detergent in the hemolyzing reagent to eliminate

interference from leukocyte. Calculation:- The Cobas c 111 analyzer automatically calculate the ratio of Hb A1c of each sample. Normal values (HbA1c%): 4.8-5.9%.

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 aneylete concentration of each sample either in $\mu\text{u/ml}$ or pmol/l . Normal value:- 2.6-24.9 $\mu\text{u/ml}$.

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 immuno assay (ECLIA) is intended for use on Elecsys and Cobas e immuno assay analyzers. Normal values :- Am 54.9-287.6 ng/ml , Pm 24.6-171.5 ng/ml .

Evaluation of insulin resistant (HOMA- IR)

The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function. It was first described under the name HOMA by (26). The approximating equation for insulin resistance used a fasting blood glucose and insulin in serum and is calculated by the following formula and can be readily done in general practice:

$$\text{HOMA-IR} = \frac{\text{Glucose mmol/l} \times \text{Insulin } \mu\text{u/ml}}{22.5}$$

Index values below 2.0 are normal, values between 2.0 and 2.2 are borderline, values between 2.2 and 3.0 indicate moderate insulin resistance, while values above 3.0 indicate severe insulin resistance.^[27]

Statistical Analysis

The Statistical Analysis System- SAS (2012),^[28] 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 AND DISCUSSION

Table (1) shows the levels of TSH μ /l and thyroid hormones T₄,T₃nmol/l (Mean \pm SE)in the study groups.

Groups	No.	Mean \pm SE		
		TSH (μ /L)	T ₄ (nmol/L)	T ₃ (nmol/L)
Patients	24	43.74 \pm 3.61	48.59 \pm 0.98	1.31 \pm 0.14
Control	24	1.97 \pm 0.264	80.12 \pm 3.09	1.52 \pm 0.083
LSD value	---	7.304 **	15.372 **	0.331 NS
P-value	---	0.0001	0.0002	0.221
** (P<0.01), NS: Non-significant.				

The TSH level (43.74 \pm 3.61) μ /L increased significantly (P<0.01) in the patients group in comparison with control group(1.97 \pm 0.264); T₄ (48.59 \pm 0.98) decreased significantly(P<0.01) in the patients group in comparison with control group(80.12 \pm 3.09); T₃ levels were not significant (p \geq 0.05) between two groups (1.31 \pm 0.14); (1.52 \pm 0.083) respectively. Our results showed Overt hypothyroidism in the patients group and were in agreement with that reported by.^[29,30,31] which characterized by elevation of TSH level, thyroxine below normal values while T₃ was within normal values.

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

Groups	No.	Mean \pm SE			
		Cortisol (ng/ml)	Insulin (μ U/ml)	Glucose (mmol/L)	HbA1c (%)
Patients	24	274.08 \pm 9.37	15.13 \pm 1.14	4.84 \pm 0.15	5.50 \pm 0.18
Control	24	174.33 \pm 13.55	8.28 \pm 0.76	4.98 \pm 0.11	5.54 \pm 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 \pm 9.37) ng/ml increased significantly (P<0.01) in the patients group in comparison with control group (174.33 \pm 13.55); Insulin (15.13 \pm 1.14) μ U/ml increased significantly (P<0.01) in patients group when compared with control group (8.28 \pm 0.76); Glucose levels mmol/l were not significant (p \geq 0.05) in patients(4.84 \pm 0.15)and control group (4.98 \pm 0.11).HbA1c% levels (5.50 \pm 0.18;5.50 \pm 0.18) in both groups were not significant(p \geq 0.05) respectively. Cortisol elevation in our study emphasizes overt hypothyroidism has been associated with subtle metabolic stress which could be imposing an effect on the Adrenocorticotrophic hormone(ACTH)–adrenal axis leading to an increase in release and production of stress hormone (cortisol).^[32] Insulin increased in patients group was in agreement with.^[33] who recorded hyperinsulinemia observed in short-term dexamethasone-

induced or corticosterone-treated rats may result from an up-regulation in glucose transporter 2 (GLUT2) receptor expression which in turn stimulates glucose-stimulated insulin secretion (GSIS).^[34] reported an elevated of insulin level in patients with diabetes or abdominal obesity which belong to hyperactivity of the hypothalamus-pituitary-adrenal axis is frequently found in hyperinsulinemic subjects with increased plasma ACTH levels; The levels of blood glucose and HbA1c% were within normal values as the hypothyroid patients in our study were non-diabetic. While.^[35] reported 20 prediabetes and 38 diabetes in 58 subclinical hypothyroidism and the conclusion of their study a positive and significant correlation between blood glucose and HbA1c.

Table(3): shows insulin resistance%, BMI kg/ m².

Groups	No.	Insulin resistance(%)	BMI (kg/m ²)
Patients	24	3.39 ± 0.29	25.81 ± 0.39
Control	24	1.81 ± 0.16	23.72 ± 0.49
LSD value	---	0.671 **	1.286 **
P-value	---	0.0001	0.0020

Insulin resistance (%) increased significantly ($P < 0.01$) in patients group (3.39 ± 0.29) in comparison with control group (1.81 ± 0.16), Figure 1. BMI index increased significantly ($P < 0.01$) in patients group (25.81 ± 0.39) in comparison with control group (23.72 ± 0.49), Figure.2

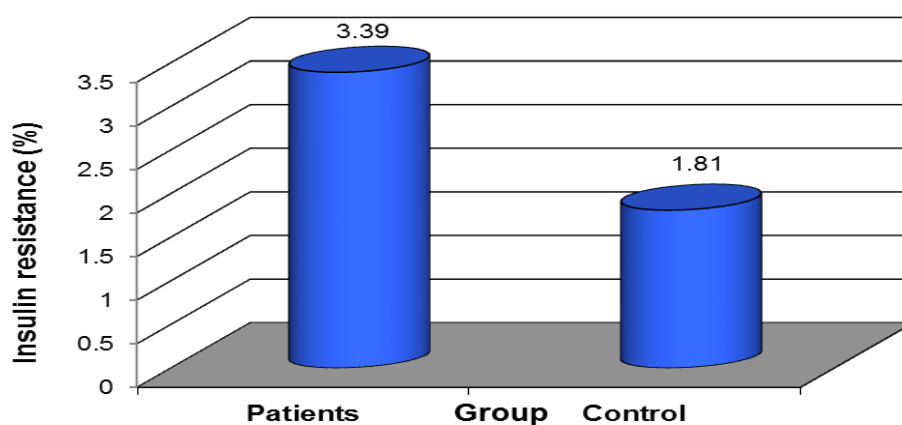


Figure1. Compare between patients & control in Insulin resistance

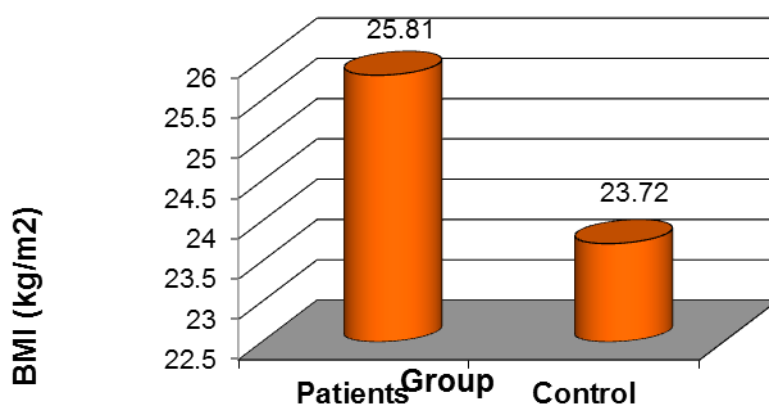


Figure 2. Compare between patients & control in BMI

The Homeostasis model of assessment (HOMA-IR) was employed to assess the level of insulin resistance.^[26] The increasing of insulin resistance in our study table(2) in overt hypothyroidism (OH) was in agreement with that reported by.^[36,37] that Subclinical (SCH) and overt hypothyroidism (OH) are established risk factors for insulin resistance, hyperlipidemia, hypercoagulability and low grade inflammation, it was found that insulin resistance was comparable in both SCH and OH; that SCH & OH hypothyroidism have shown the presence of insulin resistance in these studies due to impaired glucose disposal in peripheral tissues and hyperlipidemia. As insulin resistance refers to impaired sensitivity to insulin mediated glucose disposal.^[38] The increasing in the level of BMI in patients group may be related to an increase in body weight by increasing mucin deposits and by salt and water retention.^[39]

Table(4): shows Correlation coefficient between cortisol with TSH, T4 and T3 in the patients group.

Parameters	Correlation coefficient (r)	Level of sig.
Cortisol & TSH	0.65	**
Cortisol & T4	-0.32	*
Cortisol & T3	-0.18	NS
* (P<0.05), ** (P<0.01), NS: Non-significant.		

There is a positive correlation (0.65) between cortisol and TSH at (P<0.01) level, Figure3. While cortisol showed negative (- 0.32) correlation with T4 at (p<0.05) level, Figure4. Cortisol and T3 showed non-significant (p≥0.05) negative correlation (-0.18).

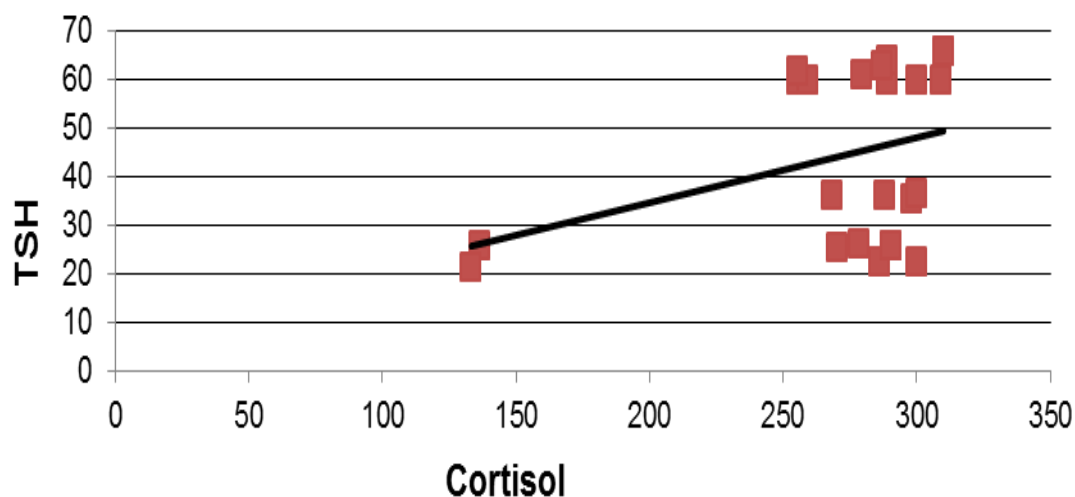


Figure 3. Relationship between Cortisol & TSH

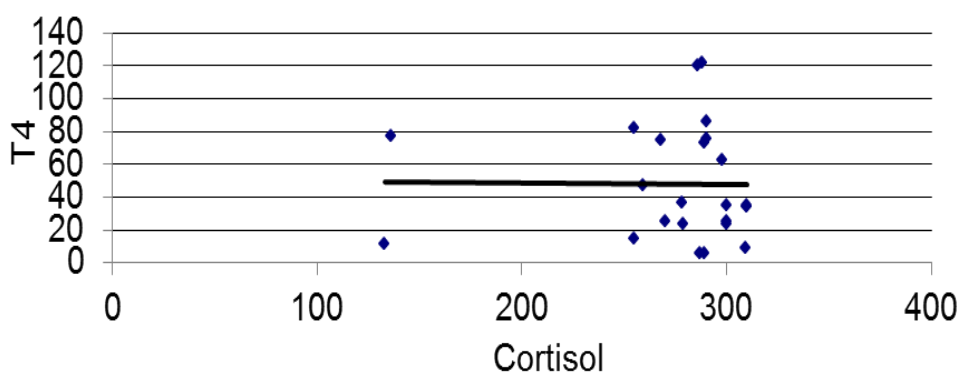


Figure4 relationship between T4&Cortisol

The potential explanation of positive relationship (0.65) between cortisol & TSH in our study table (4) that overt hypothyroidism causes elevation of cortisol by reducing peripheral disposal and blunting feedback of cortisol on the hypothalamic–pituitary–axis due to increasing TSH level.^[40] The negative relationship(-0.32) in cortisol and T4 table (4) may be due to the increasing of cortisol level which lower thyroid binding globulin (TBG) levels, the total thyroid hormone (bound and free) in the blood will be low therefore T4 will be lower^[41].

Table(5) shows Correlation coefficient between insulin resistance with glucose, HbA1C, BMI in the patients group.

Parameters	Correlation coefficient (r)	Level of sig.
Insulin resistance & Glucose	0.32	*
Insulin resistance & HbA1C	-0.08	NS
Insulin resistance & BMI	0.33	*
* (P<0.05), NS: Non-significant.		

Insulin resistance & Glucose correlation was positive (0.32) in patients group significantly ($p \leq 0.05$) Figure 5. Insulin resistance & HbA1C% in patients group showed negative (-0.08) nonsignificant ($p \geq 0.05$). Insulin resistance & BMI showed positive (0.33) significantly ($p \leq 0.05$) Figure 6.

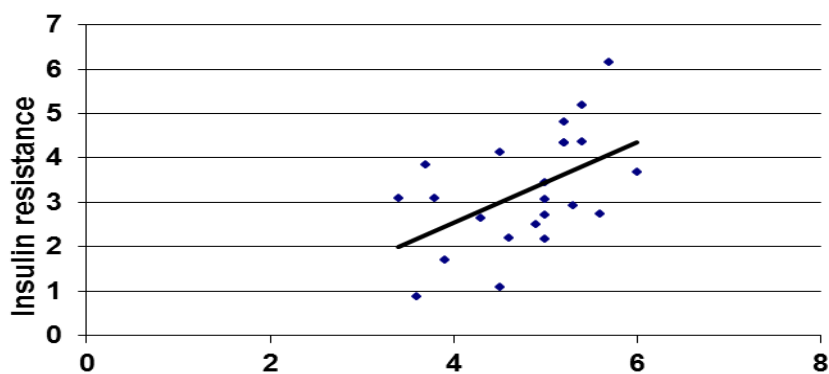


Figure 5. Relationship between Insulin resistance & Glucose

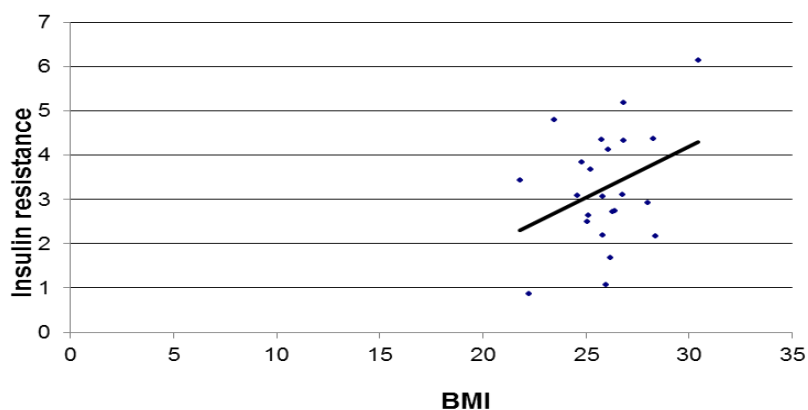


Figure 6. Relationship between Insulin resistance & BMI

The positive relationship (0.32) between insulin resistance and glucose in our result table (5) explain that Insulin resistance is a condition in which the body produces insulin but does not use it effectively. When people have insulin resistance, glucose builds up in the blood instead of being absorbed by the cells, leading to type 2 diabetes or prediabetes (NDIC).^[42] The increasing of Cortisol level in patient group table (1) induces insulin resistance probably by antagonizing the antilipolytic effect of insulin.^[43] that glucocorticoids, mediated the activation of the hypothalamic-pituitary-adrenal(HPA) axis which have an impact on metabolic responses, insulin-resistance and lipolysis.^[44] promote free fatty acid release from mature adipocytes through hormone sensitive lipase (HSL)-mediated lipolysis.^[45] That park *etal.*^[46] reported higher levels of cortisol was associated with elevated blood pressure, fasting

glucose and total cholesterol in men and women. The positive relationship(0.33)for insulin resistance & BMI reflected such antagonizing the antilipolytic effect of insulin that BMI increased in overt hypothyroid group.^[43]

Table(6)shows Correlation coefficient between BMI with TSH, T4, T3 and in the patient group.

Parameters	Correlation coefficient (r)	Level of sig.
BMI & TSH	0.39	**
BMI & T4	-0.36	**
BMI & T3	0.002	NS
** (P<0.01), NS: Non-significant.		

BMI&TSH represented significant (P<0.01) positive (0.39) correlation, Figure7. BMI & T4showed significant (P<0.01) negative (-0.36) Correlation in patients groups,Figure8.BMI & T3 showed positive (0.002) non significant ($p \geq 0.05$).

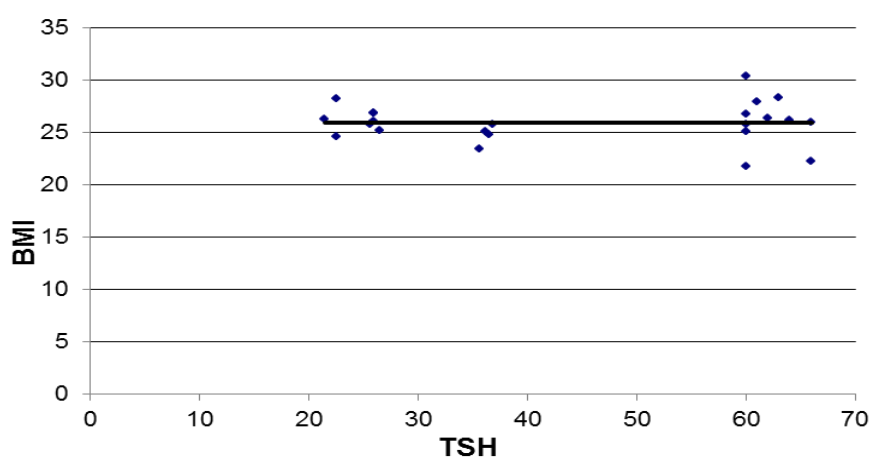


Figure 7. Relationship between BMI & TSH

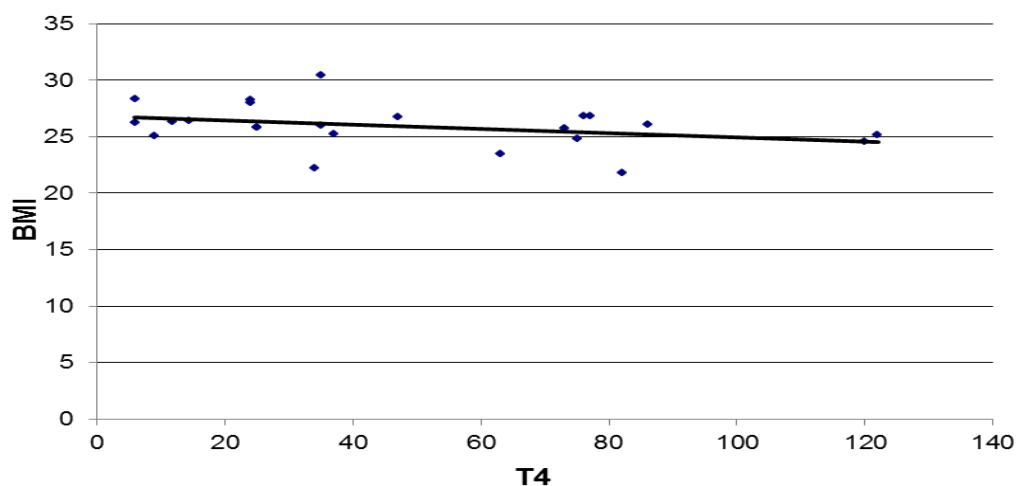


Figure 8. Relationship between BMI & T4

Our result showed that BMI was positively correlated with TSH(0.39); negatively to T4(-0.36) and had no correlation with T3 table (6) was in agreement with that reported by,^[47] Milionis and Milionis,2013,^[48] reported a positive correlation between serum leptin and TSH which also means a positive correlation between BMI and TSH that obese persons have increased level of leptin which directly stimulate TRH and leading to increased TSH Kumar *et al.*^[49] So the positive (0.39) relationship in BMI with TSH in our study table(6) increasing BMI that showed in table(3). Using BMI is popular because it is simple, quick, effective and applies to adult that Insulin resistance associated with distribution of body fat Preeth *et al.* ^[50] We concluded from our present study that such an increase in level of cortisol in the non-diabetic overt hypothyroid men patients with increasing TSH levels had contribute to elevate insulin level with increasing insulin resistance that Insulin resistance associated with distribution of body fat subsequently leading to an increase of body mass index(BMI) among hypothyroid patients through most the positive correlations relationship.

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