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RESEARCH ARTICLE

Detection for Pre- diabetes in Hypothyroid Patients

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Manuscript Info *Abstract*

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Abbreviations:

OGTT(Oral glucose tolerance test),FBG(fasting blood glucose),HOMA IR(insulin resistance),HbA1c(glycatedhaemoglobin),BMI(bodymass index)

Hypothyroidism is one of the most common functional disorders of the thyroid gland. It has long been recognized that thyroid hormone have marked effects on glucose homeostasis. Aims of the study: Study the possibility of insulin resistance and Evaluation the factors that contributes in diabetes. Materials and method: This randomized study was carried out on 60 Iraqi hypothyroid patients and apparently healthy control subjects with total number of 30 were included in this study. The two groups were subjected to receive an (OGTT) and blood sample was collected for measurement of (FBG, HOMA IR, and HbA1c %) in addition to take the BMI. Results: It seems that there is highly significant differences in the sub diffusion of Hypothyroid patients in to (diabetic group, pre-diabetic,non diabetic group) $p<0.05$ when they compared with healthy control group. In addition to a strong correlation $p<0.05$ has been found between TSH and HbA1c%, TSH and HOMA IR, TSH and BMI. Conclusion: It was concluded that patients with hypothyroidism have no possibility to control the level of sugar in the blood and hypothyroid patients may be ready to get diabetes.

Introduction

Hypothyroidism is one of the most common functional disorders of the thyroid gland (Singh *et al*.,2010). It has long been recognized that thyroid hormone have marked effects on glucose homeostasis. As it is known that glucose intolerance is associated with hyperthyroidism, and more recently it was shown that hypothyroidism is associated with insulin resistance (Shashi*et al*.,2013), which it is a pathological state in which the target cell fails to respond to ordinary levels of circulating insulin resulting in failure to maintain normal glucose and lipid levels in circulation(Nanda *et al.*,2012).

With regard to obesity hypothyroidism is frequently associated with weight gain, decreased thermogenesis, and metabolic rate (Biondi, 2010), moreover the proportions of people with type 2 diabetes and obesity have increased, and the rate of increasing shows nosign of slowing. People in tend to develop diabetes with a lesser degree of obesity at younger ages, suffer longer with complications of diabetes, and die sooner (Yoon *et al*., 2006).For all of that the objectives of this study are studying the possibility of insulin resistance in hypothyroid patients for early detection of diabetes mellitus and Evaluation the factors that contributes in inducing of insulin resistance in hypothyroid patients.

Materials and methods:

This randomized study was carried out on 60 Iraqi hypothyroid patients and apparently healthy control subjects with total number of 30 were included in this study. Their ages were between (30-60) years old. The two groups were subjected to receive an oral glucose tolerance test (OGTT) (75 gm. of glucose in 300 ml of water). The subjects were asked to fast over night following which fasting blood samples were collected. EDTA whole blood was used for the estimation of (HbA1c %), serum used for the estimation of fasting blood glucose , fasting insulin ,

In addition after one hour and tow hour thereafter blood sample obtained for estimation of glucose. BMI was measured by the individual's body mass divided by the square of their height.

Laboratory Assessment:

1-Blood glucose and HbA1c were measured by enzymatic method (Spectrum Germany).

2- Fasting insulin were measured by an enzyme immunoassay (ELIZA) (Demeditecdiagnostickit) Germany. Insulin resistance was measured by HOMAIR (Matthews*et al*.,1985).

Procedure:

Criteria for the diagnosis of diabetes were used in present study; these criteria were submitted by world health organization (WHO) and American Diabetes Association (ADA). (Niflioglu*et al.*,2012) That classified diabetes when fasting blood glucose (FBG) is (≥ 126 mg/dl), plasma blood glucose after two hours from having OGGT is (≥ 199mg/dl) and HbA1c % is (≥ 6.5 %). ; Pre-diabetes when (FBG) is between (100-125) mg/dl, (PBG) is between (140-199) mg/dl and HbA1c % is between (5.7-6.4%).

Statistical Analysis

The Statistical Analysis System- SPSS (2004) was used to effect of difference factors (concentration or strain) in study parameters. The least significant difference (LSD) test of the comparative between means in this study. The usual methods, which used in order to analysis and assess the results, they include:

-Descriptive statistics:

a- Statistical tables.

b- Graphic presentation.

Results:

Depending on the criteria of WHO and ADA there were 9 (15%) of the hypothyroid patient have diabetes and 33 (55%) are pre-diabetes and 18 (30%) does not have diabetes.

In this study it has been trying to compare some parameters such as (TSH, HOMA IR, HbA1c % and BMI) in study groups which they are (diabetes, pre- diabetes and non - diabetes) with control group and most of the results were with highly significant differences, such as the results in the table (1), where notes that there is highly significant differences (p=0.006) when compared the TSH level in diabetic group with control group, in addition it can be seen highly significant differences p=0.006 when compared the percentage of HOMA IR in diabetic groupand control group. As well as it has been found highly significant differences p=0.015, p=0.015 when compared the HbA1c%, BMI in diabetic group with control group.

According to the pre diabetic group it has been found that there is highly significant differences when compared the (TSH, HOMA IR, HbA1c%, BMI) between pre- diabetes group and control group ,where the significant differences were (p=0.00, p=0.00, p=0.014,p=0.00) respectively.Table (2).

Moreover, in this study it has been carrying out a comparable between non diabetic group and control group in each of (TSH, HOMA IR, HbA1c%, BMI), and as a result it has been found that there is highly significant differences in(TSH, HbA1c%, BMI); P=0.00, P=0.00, P=0.00 respectively .while there is no significant differences p=0.189 when compared the HOMA IR between non diabetic group and control group. Table (3).

The study of the correlation between the level of the TSH and HOMA IR(insulin resistance) in a group of patients who appeared to have diabetes as well as a group of patients who are pre-diabetes, shown there is a positive correlation because there was a significant differences $p<0.05$. r=0.88,

r=0.544 respectively. While correlation between TSH and HOMA IR in non- diabetic group, there is no significant correlation with the insulin resistance in this group .P=0.189, r=0.259. Figure (1).

The results of the relationship between the level of TSH and the proportion of hbA1c% indicate existence of significant differences in all groups of the study. It was found that the P=0.031, r=0.712 in the group of diabetes, according to the group of patients with pre-diabetes also there were highly significant differences P=0.007,r=0.469, moreover in a group of non-diabetic patients found that P=0.012,r=0.58. This indicates the presence of significant differences in this group. Figure (2).

The results of the current study were with a positive correlation, so there were highly significant differences between the TSH and BMI in Diabetes group P=0.004, moreover there were highly significant differences in Pre-diabetes group P=0.036, also found that there were significant differences reported in the group with non- diabetes P=0.015. Figure (3).

Table (1): Comparison between some studied parameters in hypothyroid diabetes group

Parameters	Diabetic group	Control	Significances
	M±SD	M±SD	
TSHµIU/ml	33.96±26.21	1.93±1.23	P=0.006** HS
HOMA IR	10.10±6.72	1.94±0.4	P=0.006** HS
HbA1c %	7.88±0.24	4.9±0.54	P=0.01** HS
BMIkg/m^2	39.55±6.22	27.5±4.4	0.015** HS

**=Highly Significant.
*=Significant.
M±SD=mean± standard deviation

Table (2): Comparison between some studied parameters in hypothyroid pre-diabetes group.

parameters	Pre- Diabetic group	Control	Significances
	M±SD	M±SD	
TSH µIU/ml	19.4±8.22	1.93±1.23	P=0.00** HS
HOMA IR	9.21±4.89	1.94±0.4	P=0.00** HS
HbA1c%	6.27±0.17	4.9±0.54	0.014** HS
BMI kg/m^2	33.21±5.08	27.5±4.4	0.00** HS

**=Highly Significant.
* =Significant.
M±SD=mean± standard deviation.

Table (3):Comparison between some studied parameters in hypothyroid non –diabetic Group.

Parameters	Non Diabetic group	Control	Significances

	M±SD	M±SD	
TSH µIU/ml	11.93±4.74	1.93±1.23	P=0.00** HS
HOMA IR	2.17 ± 0.5	1.94±0.4	P=0.189 NS
HbA1c%	5.47±0.18	4.9±0.54	0.00** HS
BMI kg/m^2	37.44±9.09	27.5±4.4	0.005** HS

**=Highly Significant.
* =Significant.
M±SD=mean± standard deviation.

The results of correlation between TSH and HOMA IR, HbA1c % and BMI were obtained through statistical analysis of coefficients of these parameters of our patients are presentedgraphically as follows:

Figure (1): Correlation between TSH and HOMA IR in diabetes mellitus group, Pre-diabetes and non diabetes group.
P=0.006, r=0.88 in diabetes.
P =0.00, r=0.544 in pre- diabetes.
p = 0.189, r =259 in non diabetes.

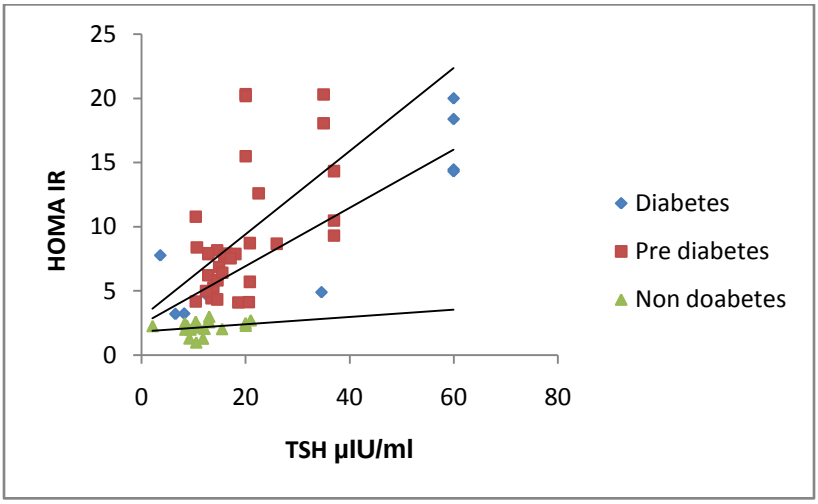
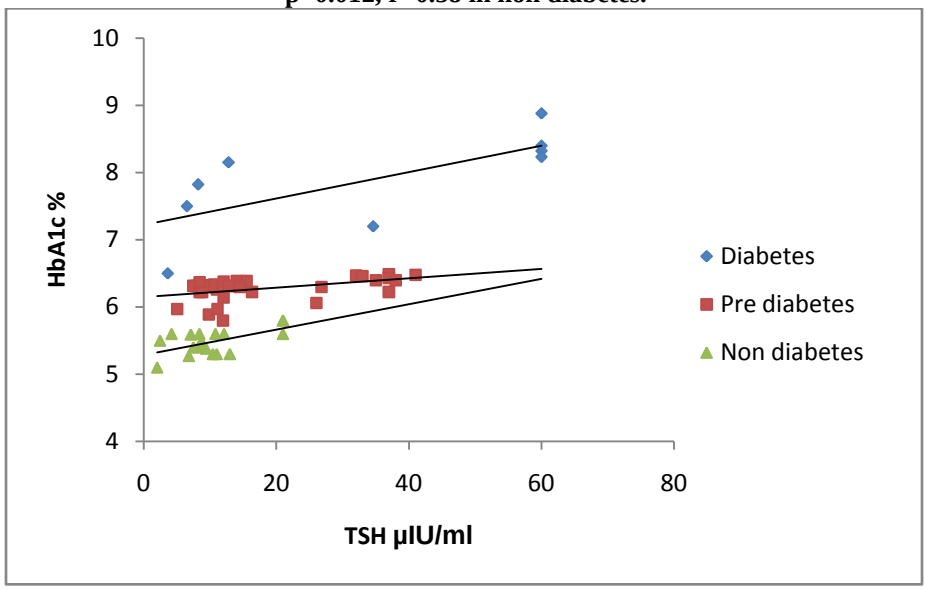
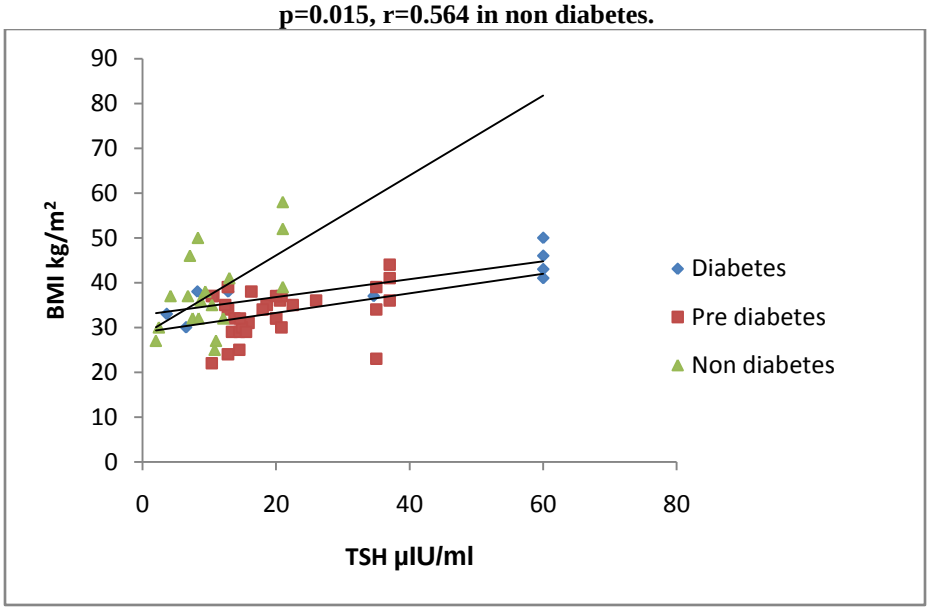


Figure (2): Correlation between TSH and HbA1c% in Diabetes, pre-diabetes and non-diabetic patients.
P=0.031, r=0.712 in diabetes.

p=0.007, r=0.469 in pre-diabetes.
p=0.012, r=0.58 in non diabetes.



Figure(3):Correlation between TSH and BMI in diabetic group, pre -diabetes and non diabetes.
p=0.004, r=0.842 in diabetes.
p=0.036, r=0.365 in pre- diabetes.
p=0.015, r=0.564 in non diabetes.



Discussion:

In this study, it has been trying to investigate the presence of diabetes in patients with hypothyroidism. Among these patients was found: 9(15%) patients with diabetes and 33(55%) patients with pre diabetes and 18 (30%) of hypothyroid patients do not have diabetes. In addition to confirming that, it has been compared the level of insulin resistance to these three groups with a control group where it has been found highly significant differences. When compared the level of insulin resistance for each of diabetes groups the (P) value was ($p<0.01$) and pre-diabetes group ($p<0.01$) with the control, while there were not significant differences when compared the non-diabetic with the control group ($p>0.05$). Table (1), In addition to that it has been carried out a study of correlation between TSH and HOMA IR (insulin resistance) and the result was that there is a positive correlation between the two parameters , This indicates that high level TSH in serum of hypothyroid patients can be a valuable cause of insulin resistance which it is a biologic state in which the target cell fails to respond to ordinary levels of circulating insulin resulting in failure to maintain normal glucose in circulating .this leads to increase insulin secretion in order to maintain normoglycaemia (Nanda *et al*.,2012 ; Eckel*et al*.,2005 ;Wang*et al*.,2004). And since hypothyroidism characterized by low concentrations of total and free thyroxine (T4) and triiodothyronine (T3) are below normal, and the concentration of thyroid-stimulating hormone (TSH) is increased (Gaby, 2004).

Since these hormones exert profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels and counter-regulatory hormones, intestinal absorption, hepatic production and peripheral tissues (fat and muscle) uptake of glucose (Brenta, 2011). It has long been known that thyroid hormones actdifferently in liver, skeletal muscle and adipose tissue – the main targets of insulin action. While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis, (Cl´ement*et al*.,2002) .They up-regulate the expression of genes such as GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin in facilitating glucose disposal and Utilization in peripheral tissues. In skeletal muscle, the main site of insulin-mediated glucose disposal, glucose transporter GLUT-4, is induced by T3, revealing that it can increase basal and insulin stimulated glucose transport in this tissue.Another mechanism, whereby thyroid hormones are known to increase hepatic glucose output, is through increased hepatic expression of the glucose transporter GLUT-2. Therefore T3 could be further aggravating the dysregulation of liver glucose characteristic of (Brenta, 2011).

With regard to the group of hypothyroid patients who did not appear to have insulin resistance , this has been found in match with another study carried out on patients with hypothyroidism and reported that there is a group of them is not ready to get diabetes . (Ibrahim, 2008). In spite of the high level of the TSH, there is no significant correlation with the insulin resistance.

A comparison was carried out between the level of glycated hemoglobin in study groups and control group and it was found that the results were with significant differences. Table (1, 2, 3) this indicates that thyroid hormone acts as important mediators of glucose homeostasis.

Although the exact mechanisms involved are still unclear,(Boelen, 2013). A comparison between BMI for each of the three groups with the control group was carried out, these comparisons characterized by the existence of significant differences between the (Diabetic group, pre-diabetic group ,non diabetic group) with the control group , suggesting that the three groups have a high body mass index, and this is attributable to the thyroid gland major role, moreover Recent studies have yielded convincing evidence that adipocytes and preadipocytes possess thyrotropin receptors (Bastemir*et al*.,2007; Sorisky*et al*.,2000; Schaffler*et al*., 2005). The signal generated by thyrotropin in adipocytes is mediated by the activation of cAMP-dependent protein kinase (Rosenbaum *et al.*, 2000). Studies in vitro and in vivo demonstrate that the action of thyrotropin via its receptors in fat tissue induces differentiation of preadipocytes into adipocytes, and expansion of adipose tissue (adipogenesis) (Valyasevi*et al.*, 2002).

The results of the correlation between TSH and HbA1c agreed to a study carried out on patients with subclinical hypothyroidism, where it found that there is a positive relationship between the level of TSH and the level of HbAa1c.(Billic-Komarica*et al*.,2012). Moreover the results in this study were identical with the results of another study carried out on a group of hypothyroid patients who have diabetes at the same time where found that The type 2 diabetic subjects with thyroid dysfunction tended to have higher levels of blood HbA1c compared with those of control. This confirms that thyroid hormones effect on blood glucose (Afkhami-ardekani*et al*.,2010). We can

concluded from this study that Patients with hypothyroidism usually have high levels of TSH, in addition it was found that these patients have a high level of insulin resistance (HOMA IR), especially those who have hormone levels higher than 15 µIU/ml. As well as patients with hypothyroidism have no possibility to control the level of sugar in the blood (HbA1c %) so it found that all patients in the study were having a high level of glycatedhaemoglobin.

Furthermore, hypothyroid patients are suffer from a rise in body mass index BMI and it is closely linked with the TSH level, the results of the current study are identical to the study carried out by (Yap &Jasul, 2012; Kumar *et al*., 2008) was observed that a positive correlation between TSH levels and BMI. In addition, similar findings were reported that there is a positive correlation between varying degrees of obesity and varying TSH levels (Knudsen *et al.*, 2005). Earlier studies, also observed an association between BMI and TSH levels, showing varying TSH levels depending on the degree of obesity from mild to severe (Iacobellis*et al.*,2005).

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