Original Article

Glycemic Status in Patients with Primary Hypothyroidism and its Relation to Disease Severity

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Abstract

Background: Primary hypothyroidism can be defined as an increase in serum thyroid-stimulating hormone (TSH) level, and the concentration of free T3, free T4, T3, and T4 is low. Hypothyroidism is a prevalent disease mostly affecting middle-aged women. One of the most important determinants of glucose homeostasis is thyroid hormones. Hypothyroid patients have a higher prevalence of insulin resistance and tendency to Type 2 diabetes mellitus than the normal individual. **Objective:** To investigate the correlation between TSH and hemoglobin A1c (HbA1C) in patients with primary hypothyroidism; so, to study the effects of hypothyroidism on glucose metabolism. **Subjects and Methods:** Ninety-five Iraqi primary hypothyroidism patients and 40 healthy persons taken as control were selected from Specialized Centre for Endocrinology and Diabetes during the period from June 2017 to January 2018. The patients were diagnosed previously as cases of primary hypothyroidism, and they were on treatment and still on treatment. All patients were sent to investigate TSH, T4, T3, and HbA1c. The patients were subdivided into three main groups: first is uncontrolled nondiabetic primary hypothyroid group (36 patients), second is controlled nondiabetic primary hypothyroid group (43) and third is the diabetic primary hypothyroid group (16 patients). **Results:** A significant difference ($P < 0.05$) between HbA1C% in both controlled and uncontrolled hypothyroid groups against the control group, but there is no significant difference ($P = 0.08$) between the controlled and uncontrolled hypothyroid groups. The TSH relation with HbA1c was found to be significantly positive in the uncontrolled hypothyroid and diabetic, hypothyroid groups ($r = 0.401$ and 0.58, respectively). **Conclusions:** Significant increment was found in the level of HbA1c in hypothyroid patients, whether it is controlled or uncontrolled and a positive relationship was observed between TSH and HbA1c% in the uncontrolled and diabetic hypothyroid groups. Diabetes augments the effects of hypothyroidism on HbA1c.

Keywords: Glycemic status, insulin resistance, primary hypothyroidism

Introduction

Primary hypothyroidism

The central feature of hypothyroidism is the reduced production of thyroid hormone.[1,2] Its prevalence increases with age, and the disease in women is about ten times more common than men. Hypothyroidism is more common in areas where there is iodine deficiency. Individuals who are at increased risk for developing hypothyroidism are those who have positive thyroid peroxidase antibodies and who have thyroid-stimulating hormone (TSH) values in the upper normal range.[3] Hypothyroidism affects carbohydrate metabolism in different ways:

- First: It has been found that the thyroid hormone stimulates expression of the insulin-sensitive glucose transporter (GLUT4), so in hypothyroidism the levels of this transporter are usually low
- Second: The activity of prohormone processing enzymes are increased in hypothyroidism, and this happened because one of important function of thyroid hormone, is downregulation of expression of these enzymes and this will lead to the slowing of degradation of insulin and increasing sensitivity to exogenous insulin. Hence, when hypothyroidism happened in patients with preexisting diabetes, there is a decrease in insulin requirement

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- Third: Hypothyroidism may affect glucose uptake at the tissue level. Local T3 production may be affected by polymorphisms in the 5-deiodinase type 2 (D2) genes, which may occur in hypothyroidism and decrease glucose uptake by tissues.[4]

The general changes in hypothyroidism will be reduced absorption of glucose from the gastrointestinal system, accumulation of glucose in peripheral tissues, the process of gluconeogenesis will be slowed, the output of glucose from the liver will diminish and increase tissue resistance to insulin entrance (i.e., increase insulin resistance).[5] The relationship between diabetes mellitus (DM) and thyroid dysfunction was found to be very strong.[6] Hypothyroidism (Hashimoto's thyroiditis) or thyroid hyperactivity (Graves' disease) has been investigated to be associated with DM. The frequency of thyroid dysfunction in the patients of DM about 11%.[7] It was found that thyroid disorders are increasing with age, and this happened globally, and all over the world, thyroid disease are less common in men than women. Subclinical hypothyroidism is reported to occur in about 4%–8.5% and may be reach 20% in females older than 60 years, while subclinical hyperthyroidism occurs less frequently and is reported to be about 2%.[8] In hypothyroidism, insulin resistance is proved and curtained in various *in vitro* and preclinical studies.[9-11]

It was found that the responsiveness of peripheral muscles to insulin action in hypothyroid patients became less. The dysregulation of metabolism of leptin could be responsible for such pathology.[11]

Many authors are document a direct relationship between insulin resistance and hypothyroidism.[12-15] The insulin resistance not just associated with overt hypothyroidism but also with subclinical hypothyroidism[14,16,17]

Subjects, Materials and Methods

Our study is a cross-sectional study and was done among 95 patients of diagnosed hypothyroidism from The Specialized Centre for Endocrinology and Diabetes and 40 persons who tested negative for thyroid disorder and they are not using any type of medication, with no mental or physical abnormality and no chronic disease was diagnosed previously, were taken as control for the study between the months June 2017 and January 2018, with an age range between 18 and 65 years. The patients were diagnosed previously based on the level of T3, T4 and TSH and they were on treatment and they were still on it during the study period.

Inclusion criteria

1. Patient who already diagnosed previously as a case of primary hypothyroidism and on thyroxin treatment
2. Patients who accept participation.

Exclusion criteria

1. History of pituitary or hypothalamic disease or surgery
2. Renal failure or dialysis
3. Pregnant hypothyroid patient
4. Any haemoglobinopathy
5. Hemolytic disorder
6. Recent (<3 months duration) blood transfusion.

All patients were sent for the following investigations:

1 – TSH 2 – Hemoglobin A1c (HbA1c%): We used the GX assay Kit, which used exclusively with the Tosoh Automated Glycohemoglobin Analyzer HLC-723 GX referred to as HLC-723GX in the IFU), which is based on the principle of high-performance liquid chromatography assay.

Statistical analysis

Results were presented as mean ± standard deviation for quantitative variables, and it was done by Statistical analysis were performed using MedCalc for windows, version 15.0 (MedCalc Software, Ostend, Belgium) and by the same program *P* value was calculated:

$P < 0.05 \rightarrow$ significant $P > 0.05 \rightarrow$ not significant.

Filtration of the results and figures was done by the excel program.

Correlation of the results (Pearson's correlation coefficient) was done by IBM Corp. Released 2015. IBM SPSS Statistics for windows, version 23.0 Armonk, NY: IBM Corp.

The patients were subdivided into three main groups according to the controlling of thyroid status based on TSH results and according to the presence of diabetes:

- First group: Uncontrolled, not diabetic overt hypothyroidism this group comprised (36 patients) (TSH between 5.6 and 53.3 mU/L)
- Second group: Controlled not diabetic hypothyroidism (43 patients) (TSH between 0. 5 and 4.5 mU/L)
- Third group: Diabetic hypothyroidism (16 patients).

Results

HbA1c levels in uncontrolled overt hypothyroid group were found to be in a range of 4.8%–6.3% with a mean of 5.78 ± 0.806 against the range of 4.8%–6.2% with the mean of 5.28 ± 0.45 in the healthy control group. The difference was found to be highly significant ($P = 0.0012$), while HbA1c in the uncontrolled hypothyroid group is not statistically different against HbA1c in controlled hypothyroid group were in the range of 4.9%–6.3% with the mean of 5.532 ± 0.452 ($P = 0.082$). All these findings are summarized in Table 1.

HbA1c level in controlled hypothyroid group were found to be in a range of 4.9%–6.3% with a mean of 5.532 ± 0.452 against the range of 4.8%–6.2% with the mean of 5.28 ± 0.45 in the healthy control group and the difference was found to be significant ($P = 0.014$) and at the same time HbA1c in the diabetic, hypothyroid group were found to be in a range of 6%–13.7% with a mean of 9.262, and it is higher in that of controlled hypothyroid patients and significantly different ($P < 0.0001$).

Table 1: The comparison of age, thyroid-stimulating hormone, hemoglobin A1c in the uncontrolled overt hypothyroidism group with control group and also with controlled hypothyroidism group

Parameter	Mean±SD		*P*	Controlled hypothyroid group (mean±SD)	*P*
	Uncontrolled hypothyroid group	Control healthy group			
Age	43.86±12.05	34.82±12.08	0.0017	44.348±13.587	0.86
TSH	19.06±14.94	2.07±1.02	<0.001	2.459±1.256	<0.0001
HbA1c	5.7861±0.8064	5.280.45	0.0012	5.532±0.452	0.082

SD: Standard deviation, TSH: Thyroid-stimulating hormone, HbA1c: Hemoglobin A1c

Table 2: The comparison of age, thyroid-stimulating hormone, and hemoglobin A1c in the controlled hypothyroidism group with healthy control group and also with diabetic hypothyroid group

Parameter	Mean±SD		*P*	Diabetic hypothyroid group (mean±SD)	*P*
	Controlled hypothyroid group	Control healthy group			
Age	44.34±13.58	34.82±12.08	0.0012	49.687±8.852	0.1507
TSH	2.4591±1.256	2.07±1.02	0.13	8.71±9.762	0.0001
HbA1c	5.5326±0.4523	5.28±0.45	0.014	9.262±2.835	<0.0001

SD: Standard deviation, TSH: Thyroid-stimulating hormone, HbA1c: Hemoglobin A1c

These findings are summarized in Table 2.

When we studied the correlation between TSH and HbA1c, it was found to be a weak positive correlation in the healthy control group and controlled hypothyroid group. However, there is a significant positive linear correlation between TSH and HbA1c in the uncontrolled nondiabetic hypothyroid group ($r = 0.401$, strength of correlation: medium) and also in the diabetic hypothyroid group ($r = 0.585$, strength of correlation: strong).

These relations are shown in Table 3 and Figures 1, 2, respectively.

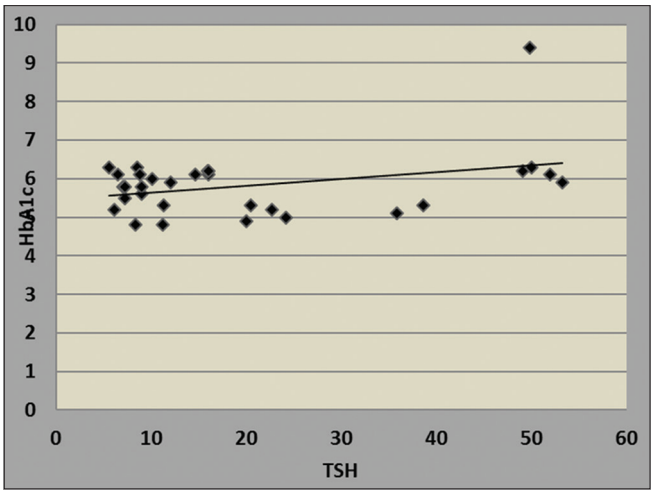

Figure 1: Correlation between thyroid-stimulating hormone and hemoglobin A1c percentage in nondiabetic uncontrolled hypothyroidism group ($r = 0.401$)

Discussion

The results of the present study showed that by comparison between HbA1c% for both uncontrolled and controlled hypothyroid nondiabetic groups against A1c in the healthy control group were found to be that it is higher with a significant difference ($P = 0.001$ and 0.01 respectively) when compared with the control group [Tables 1 and 2].

The result of the relationship between the level of TSH and the HbA1c% showed that there is a significant positive correlation in the uncontrolled hypothyroid group ($r = 0.401$ level of strength: medium) [Table 3 and Figure 1]. The TSH and A1C correlation in the diabetic hypothyroid group also positive, $r = 0.58$ level of strength: strong) [Table 3 and Figure 2]. These relations were found to be weak in the controlled hypothyroid group.

These results indicate that thyroid hormones act on glucose homeostasis as an important mediator although the mechanism that causes this increase in HbA1c in hypothyroid patients is still unclear.[18]

Many theories were put on to explain the dysglycemia that happens in hypothyroidism:

1. Thyroid hormones are important for glucose homeostasis and for glucose absorption, so in hypothyroidism decrease absorption leads to decrease utilization and this leads to increase in insulin level and increase resistance to insulin that will contribute to the elevation of blood glucose[19]
2. Insulin resistance is the cause of blood glucose elevation in hypothyroidism, the accepted explanation for insulin resistance mechanism is that insulin hormones work synergically with thyroid hormone to exert its action such as up regulation of genes such as GLUT4 that used in glucose transport and phosphor glycerate kinase that involved in the process of glycolysis. Therefore, in hypothyroidism, the peripheral tissue showed resistance to insulin action[20,21]
3. Thyroid hormones have an important role at the cellular level by increasing mitochondrial biogenesis, activation of Tricarboxylic acid cycle (TCA) cycle and oxidation of fatty acid.

Table 3: Comparison and correlation between thyroid-stimulating hormone and hemoglobin A1c (%) in different study groups

Study group	Number of patients	Mean±SD		*R*
		TSH	HbA1c (%)	
Control healthy group	40	2.07±1.02	5.28±0.45	0.094
Uncontrolled hypothyroidism group	36	19.06±14.94	5.78±0.80	0.401*
Controlled hypothyroidism group	40	2.45±1.25	5.53±0.45	0.166
Diabetic hypothyroidism group	16	8.71±9.76	9.26±2.83	0.585**

SD: Standard deviation, TSH: Thyroid-stimulating hormone, HbA1c: Hemoglobin A1c, **Refers to positive Pearson correlation with strong strength, *Medium strength

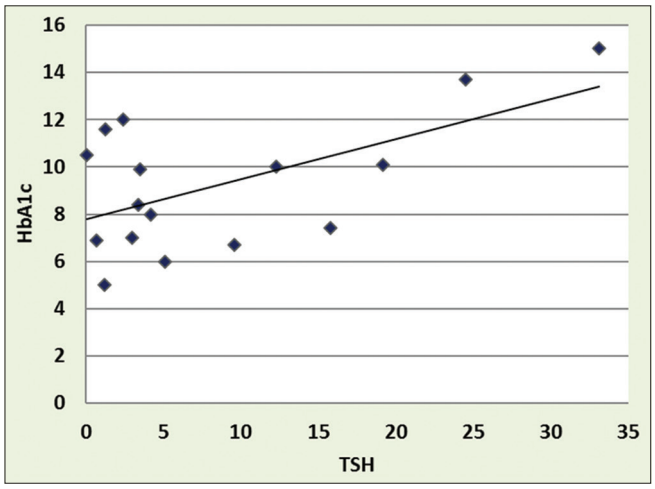

Figure 2: Thyroid-stimulating hormone and hemoglobin A1c percentage correlation in diabetic hypothyroidism group ($r = 0.585$)

In Type 2 diabetes, clearly demonstrated that the role of mitochondrial dysfunction leading to the accumulation of cellular lipid and oxidative metabolism impairments. Also, in skeletal muscle, it was found that the lack of thyroid hormones may lead to dysregulation of mitochondrial gene expression.

The transcriptional regulator of mitochondrial content and function is the PPAR gamma coactivator-1alpha (PGC-1alpha) and this regulator plays an essential role in the oxidation of fatty acid and in gluconeogenesis.

This PGC-1 that involved in the regulation of mitochondrial function requires thyroid hormone for its action. When give T3 treatment, PGC-1alpha gene expression increased by as much as 13 folds 6 h posttreatment, so in hypothyroidism decrease in the level of T3 lead to PGC1 alpha dysregulation and this lead to insulin resistance.[22]

4. Hypothyroidism leads to decrease basal metabolic rate, so this leads to decrease in protein turnover that's mean prolongation of half-life
5. Hypothyroidism is a state of increased oxidative stress that may lead to increased protein glycation.[19]

In this study, any of these theories can be applied as a cause of increase HbA1c and could be there is another factor that is responsible so difficult to differentiate the causative agent of increment A1c.

These relations had been demonstrated by another studies like a study of 45 hypothyroid patients in which HbA1c was higher than that of control (5.54 ± 0.43% vs. 5.34 ± 0.31% in hypothyroid patients and control respectively $P < 0.001$).[23]

Another study done by (Billic-Komarica *et al*. 2012) demonstrated the positive relationship between the level of TSH and HbA1c%.

In our study, the difference in HbA1c% in the uncontrolled and controlled hypothyroid group were found to be not significant ($P = 0.08$) [Table 1] and as it was mentioned both groups were found to be significantly different from the healthy control group ($P = 0.001$ and 0.01 respectively), so this raises a question, why controlling of hypothyroidism by thyroxin does not reversing the increment in HbA1c to the level of healthy control group? Is the insulin resistance could be responsible for this increase in HbA1c is irreversible?

The correct answer was not clear, but this may be the changes that occur at the cellular level that lead to great damage that even with correction not returning to the normal state. Another possible effect is the suggestion that hypothyroidism could be falsely increasing the HbA1c levels as a study in India suggest.[24] This subject needs further studies for full explanation.

Conclusions

A significant increment was found in the level of HbA1c in hypothyroid patients, whether its controlled or noncontrolled and a positive relationship was observed between TSH and HbA1c% in the uncontrolled group.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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