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DOI: 10.21767/2347-5447.1000308

# The Fasting Serum Insulin and Glucose Levels and the Estimated Insulin Resistance in Clinical and Subclinical Hyperthyroid Patients from Saudi Arabia

### **Abdel-Gayoum AA\***

Department of Clinical Laboratory sciences, Faculty of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia

\*Corresponding author: Abdel-Gayoum AA, Department of Clinical Laboratory sciences, Faculty of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia, Tel: +966565714884; E-mail: aabdelgayoum@hotmail.com

Received date: December 13, 2017; Accepted date: December 21, 2017; Published date: December 30, 2017

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**Citation:** Abdel-Gayoum AA (2017) The Fasting Serum Insulin and Glucose Levels and the Estimated Insulin Resistance in Clinical and Subclinical Hyperthyroid Patients from Saudi Arabia. Br Biomed Bull 5: 308.

# Abstract

**Introduction:** Hyperthyroidism is associated with insulin resistance, whereas its effect on pancreatic insulin secretion is controversial. The present study was aimed to investigate the influence of hyperthyroidism on the insulin availability and sensitivity and their correlations with the thyroid hormones in patients from Hail region in Saudi Arabia.

**Material and methods:** The study was conducted on patients with thyroid disorders who were visiting the Diabetic and Endocrinology Unit of King Khalid Hospital, Hail, Saudi Arabia between April 2015 and July 2015. A total of 43 newly diagnosed hyperthyroid patients (age range: 18-77 years) were classified into:

- Subclinical hyperthyroid (SHR) group: with serum TSH<0.40 mU/L and with normal FT<sub>4</sub>
- Overt Hyperthyroid (OHR) group with TSH<0.40 mU/L and FT<sub>4</sub>>25.0 pmol/L
- Control (C) group of normal subjects

**Results:** The fasting serum insulin levels in the SHR and OHR groups were severely raised by 6.22-fold and 7.67-fold, and the serum glucose by 28.76% and 54.79%, respectively compared to control, whereas, the kidney function was not altered in any of the groups. On the other hand, there were significant correlations between TSH and insulin levels (r=-0.79, P=0.0001), FT<sub>4</sub> and insulin (r=0.34, P=0.03), TSH and insulin resistance (r =-0.5, P=0.001) and between TSH and insulin sensitivity index (r=0.90, P=0.000).

**Conclusion:** Both clinical and subclinical hyperthyroid patients had significantly elevated fasting serum insulin and glucose levels and increased insulin resistance. Significant correlations exist between TSH and  $T_4$  with insulin levels, and between TSH with insulin resistance. The hyperthyroidism had no detrimental effects on the renal function.

**Keywords:** Hyperthyroidism; Hyperglycemia; Insulin resistance; Kidney function

### **Abbreviations:**

FT<sub>4</sub>: Free Thyroxine; FT<sub>3</sub>: Free Triiodothyronine; TSH: Thyroid Stimulating Hormone; HOMA-IR: The Homeostasis Model Assessment-Insulin Resistance; QUICK-I: The Quantitative Insulin Sensitivity Check Index; eGFR: Estimated Glomerular Filtration Rate

## Introduction

The thyroid hormones,  ${\rm T}_3$  and  ${\rm T}_4,$  enhance body metabolism by activating peripheral glucose oxidation and facilitating the release of free fatty acids into circulation [1]. They influence these activities by regulating the synthesis and activation of membrane transporter proteins, deiodinase enzymes, and their cellular receptors [2]. Beside their effects on the metabolic pathways, thyroid hormones are also known to regulate insulin secretion and action [3]. However, they may counteract the action of insulin by stimulating the hepatic gluconeogenesis and glycogenolysis and up-regulate the expression of hepatic glucose transporters that accelerate the hepatic glucose output [4]. Thus, the prevalence of thyroid disorders among diabetic patients is known to be significantly higher than in the general population [5] and about 16% of Saudi diabetic patients were found to have thyroid dysfunction [6]. This indicates a significant interplay between the thyroid hormone action and insulin sensitivity. Hyperthyroidism is associated with metabolic disturbances that include increased rate of basal metabolism, thermogenesis and insulin resistance [7].

The insulin resistance is characterized by impaired physiological response of peripheral tissues to insulin and is commonly associated with obesity, essential hypertension and fatty liver [8,9]. Some studies have indicated the occurrence of insulin resistance in subclinical hyperthyroid patients as well [10]. Moreover, hyperthyroidism is believed to enhance the rates of hepatic glucose production and its release into circulation by the increased expression of the hepatic membrane glucose transporter isozymes -2 and -4 [11]. From literature survey, the studies investigating the association of altered insulin sensitivity with hyperthyroidism in Saudi patients is scarce. Thus, in the present study we aimed to investigate the

influence of clinical and subclinical-hyperthyroidism on the insulin availability and sensitivity and their correlations with the thyroid hormones in patients from Hail region in Saudi Arabia.

# **Patients and Methods**

### **Protocol of study**

The study was conducted on patients with thyroid disorders who were visiting the Diabetic and Endocrinology Out-Patient Unit of King Khalid Hospital, Hail, Saudi Arabia between April 2015 and July 2015. This is the main hospital in Hail city and most of the patients from the whole region are referred to it. Thus, the patients recruited for the study are thought to represent the Hail population. The patients clinical data entered in the record book of the laboratory were used in this study. A total of 43 newly diagnosed hyperthyroid patients were recruited for the study. Depending on their serum TSH and free  $T_4$  (FT<sub>4</sub>) levels, the patients were classified into:

- Subclinical hyperthyroid (SHR) group: n-24 patients (M=7, F=17) with serum TSH<0.40 mU/L and with normal FT<sub>4</sub> levels (9.0-25.0 pmol/L).
- Overt hyperthyroid (OHR) group: n=15 patients (M=4, F=11) with TSH<0.40 mU/L and FT<sub>4</sub>>25.0 pmol/L
- The control (C) group: n=16, (M=6, F=10) were normal subjects visiting the clinic for routine check-up.

All patients had an age range of 18-77 years (mean age was  $34.47 \pm 11.20$  years). The patients had not taken insulin or other medications for a minimum of 10 hours prior to the blood sample collection. Hypothyroid, diabetic and patients with chronic diseases were excluded. 5 ml venous blood was collected from each patient after an overnight fast and serum was separated and used for the biochemical analysis. The protocol of experiment was explained and the consent was obtained from the participants. The study was approved by the ethical committee, Faculty of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia.

#### **Biochemical assays**

The concentrations of serum FT<sub>3</sub>, FT<sub>4</sub>, TSH and insulin were assayed by Auto-analyzer (ELecsys 2010, Cobas E 411-Mannheim Germany). The serum glucose, urea, creatinine, uric acid, were measured by the automated spectrophotometer, Hitachi-717, utilizing commercial kits supplied by Roche Diagnostic, United Kingdom. The estimated insulin sensitivity (QUICK-I) was calculated as described by Katz et al. [12]. Whereas, the homeostasis model assessment-Insulin resistance (HOMA-IR) index was calculated by the method described by Sarafidis et al. [13]. The values higher than 2.5 indicated insulin resistance [14].

#### **Statistical analysis**

The presented data are means  $\pm$  SD. The significance of differences between the means was computed by one way analysis of variance, followed by Multiple Comparison Analysis. Spearman's regression analysis was used to study the significance of correlation among the FT<sub>4</sub>, FT<sub>3</sub>, TSH, HOMA,

insulin, glucose and kidney function parameters. P-value less than 0.05 was considered.

### Results

As shown in Table 1, there was no significant difference in the means of ages between the three groups. The TSH of SHR and OHR groups were significantly lower than that of the control by 95.21% and 98.69%, respectively. Moreover, the  $T_4$  level of the OHR group was higher than that of the control by 1.23-fold, whereas that of SHR was not different from control. Similarly, the FT<sub>3</sub> values of the SHR group were not different from the control, whereas, that of OHR was higher than control and SHR by 56.14% and 64.47%, respectively (Table 1).

**Table 1:** The age and thyroid function parameters in subclinical hyperthyroid (SHR), overt hyperthyroid (OHR) and control (C) groups [Presented results are mean  $\pm$  SD; \*P<0.05, \*\*P<0.01, \*\*\*P<0.001; a significantly different from c, b significantly different from SHR].

	С	SHR	OHR
Age (Yrs)	33.87 ± 17.32	43.05 ± 8.83	37.64 ± 14.66
TSH (µIU/L)	2.30 ± 0.21	0.11 ± 0.01 a***	0.03 ± 0.02 a <sup>***</sup> b <sup>*</sup>
FT4 (pmol/L)	15.23 ± 3.21	18.14 ± 4.62	34.02 ± 2.62 a***b***
FT3 (pmol/L)	5.13 ± 1.22	4.87 ± 1.13	8.01 ± 0.94 a <sup>*</sup> b <sup>*</sup>

As depicted in Table 2, the fasting serum insulin levels in the SHR and OHR groups were severely raised by 6.22-fold and 7.67-fold, respectively compared to control and that of OHR by 19.95% compared to SHR (Table 2).

**Table 2:** The fasting serum glucose, insulin levels, insulin resistance (HOMA-IR) and insulin sensitivity index (QUIC-1) in subclinical hyperthyroid (SHR), overt hyperthyroid (OHR) and control (C) groups [Presented results are mean  $\pm$  SD; \*P<0.05, \*\*P<0.01, \*\*\*P<0.001; a significantly different from c, b significantly different from SHR].

	С	SHR	OHR
Insulin (mIU/L)	4.09 ± 0.44	29.57 ± 3.74 a***	35.47 ± 4.28 a***b*
Glucose (mmol/L)	5.11 ± 1.18	6.28 ± 1.04 a <sup>*</sup>	7.91 ± 1.16 a***b*
HOMA-IR	0.95 ± 0.34	8.62 ± 1.56 a***	8.42 ± 2.06 a***
QUICK-1	0.39 ± 0.06	0.28 ± 0.07 a***	0.28 ± 0.02 a***

However, the fasting serum glucose concentration was slightly raised in the SHR by 28.76% and significantly elevated in the OHR group by 54.79% compared to control. Table 3 summarizes the kidney function parameters in the hyperthyroid patients. Interestingly, none of the kidney function parameters was altered in any of the experimental groups although a slight trend of increase was observed in the uric acid levels of SHR and OHR groups, but were not statistically significant (Table 3).

 Table 3: The serum levels of kidney function parameters in subclinical hyperthyroid (SHR), overt hyperthyroid (OHR) and

control (C) groups [Presented results are mean  $\pm$  SD; \*P<0.05, \*\*P<0.01, \*\*\*P<0.001; a significantly different from c, b significantly different from SHR].

	С	SHR	OHR
Urea (mmol/L)	4.40 ± 1.02	4.26 ± 0.92	4.10 ± 0.87
Creatinine (µmol/L)	64.51 ± 8.22	68.22 ± 7.32	63.62 ± 9.19
eGFR (ml/min/)	111.87 ± 20.39	97.04 ± 19.69	103.80 ± 16.23
Uric acid (µmol/L)	227.80 ± 24.49	257.56 ± 25.24	269.78 ± 19.17

As shown in Figure 1, the regression analysis showed a significant negative correlation between age and eGFR (r=-0.37, P=0.013) but not between age and the insulin resistance index.



**Figure 1:** The straight line plots of the regression analysis (A): between serum TSH values and HOMA-IR; (B): between the values of T4 and HOMA-IR; (C): between T4 and insulin; (D): between TSH and insulin; (E): between TSH and eGFR; (F): between age and eGFR.

However, a significant negative correlation was observed between TSH and insulin (r=-0.79, P=0.0001), and a significant positive correlation between FT<sub>4</sub> and insulin (r=0.34, P=0.03). Moreover, a significant negative correlation was shown between TSH and HOMA-IR (r=-0.5, P=0.001), but not between T<sub>4</sub> and HOMA-IR. A highly significant positive correlation was evident between TSH and the estimated insulin sensitivity index (QUICK) (r=0.90, P=0.000), but not between FT<sub>4</sub> and QUICK. However, there was a trend of correlation between TSH and eGFR but was not significant (r=0.30, P=0.06). No correlation was exhibited between  $\mathrm{FT}_4$  and eGFR, or between TSH and creatinine or uric acid (Figure 1).

## Discussion

The effect of hyperthyroidism on the pancreatic insulin secretion is controversial. Some authors have reported depressed plasma insulin secretion in the hyperthyroid patients [15,16], whereas others have reported normal or enhanced secretion [17,18]. In the present study we observed a several fold increase in the fasting serum insulin levels in the overt and subclinical-hyperthyroid patients. This controversy in the circulating insulin concentration may be attributed to the varying rates of insulin catabolism in these patients [19]. It has been reported that exposure of immature pancreatic islets of the rat to thyroid hormones enhanced their maturation and secretion of the glucose-responsive insulin [20], and induced the expression of thyroid hormone-receptors and deiodinase enzymes [21]. Our results also exhibited increased insulin resistance and significantly elevated serum glucose levels in both clinical and subclinical hyperthyroid groups. These findings were in congruence with the reports of those who indicated the presence of insulin resistance and impaired glucose tolerance in hyperthyroid human and in experimental animals [10,17].

The observed hyperglycemia associated with the hyperthyroidism in spite of the high levels of circulating insulin may be attributed to one or more of several metabolic changes. First: Hyperthyroid patients have been shown to have increased circulating pro-insulin than active insulin levels and had reduced C-peptide levels compared to their euthyroid counterparts, suggesting an underlying defect in the proinsulin processing [18]. Second: The hyperthyroid patients are believed to have enhanced intestinal glucose absorption due to the increased expression of intestinal membrane glucose transporters [22,23]. Third: Increased rate of gluconeogenesis and hepatic glucose output by the expression of the hepatocyte membrane GluT<sub>2</sub> [24]. Fourth: Enhanced lipolysis and increased release of free fatty acids for oxidation and production of glycerol used for gluconeogenesis [25].

Moreover, some reports have indicated elevated intracellular calcium concentration in these hyperthyroid patients due the excessive cellular  $T_3$  content [10]. It is believed that the elevated cellular  $T_3$  content can increase the cytosolic calcium concentration [26] that may cause a calcium-induced insulin resistin [27]. Furthermore, these patients are known to have significant elevation in the levels of resistin, an insulin antagonizing adipocytokine that may enhance the development of insulin resistance [28]. All or part of these events may have played a role in the development of the observed insulin resistance and hyperglycemia.

An interesting finding in the present study was the strong positive correlation between the serum TSH and insulin sensitivity (r=0.90, P=0.000), and a negative correlation with insulin resistance (r=-0.50, P=0.001), whereas, no correlation was observed between the thyroid hormones and insulin resistance. However, both TSH and  $T_4$  had significant correlations with the serum insulin levels. These findings

indicate that thyroid hormones and thyrotropin play a role in regulating the mechanisms that enhance the insulin secretion whereas; only TSH seems to influence the insulin resistance. Our results were in accordance with the reports that indicated a positive correlation of TSH with the fasting and postprandial insulin concentrations following an oral glucose tolerance test [29], and the normal free thyroxin levels showing a significant association with insulin resistance [30]. In contrast to our finding, Javed et al. [31] observed a negative correlation between TSH and insulin sensitivity in the euthyroid male subjects. The discrepancy may be attributed to the fact that our study involved hyperthyroid male and female patients whereas their finding was in euthyroid male subjects. This indicates a possible influence of gender in this correlation.

The present results also indicated that the kidney function was not altered in any of the clinical or subclinical patients and none of the thyroid hormones or TSH had significant correlations with the estimated GFR. Thyroid hormones are known to maintain the renal function by increasing the renal blood flow and the GFR. Thus, hypothyroidism is associated with reduced GFR whereas; hyperthyroidism results in increased GFR as well as activation of the renin-angiotensin-aldosterone system [32]. In a previous study from this laboratory, we observed significantly impaired kidney function of patients with overt hypothyroidism [33]. Although, hyperthyroidism is usually not associated with kidney disease but has been shown to accelerate an initiated disease [34]. Limitations of the present study were the relatively small sample size and that the anthropometric measurements were not recorded. However, the present findings may form bases for a future investigation in the Hail region that takes the gender variance into consideration.

## Conclusion

The clinical and subclinical hyperthyroid patients had significantly elevated fasting serum insulin and glucose levels. Both groups of patients exhibited significantly increased insulin resistance. Significant correlations exist between TSH and  $T_4$  with insulin level, and between TSH with insulin resistance. The hyperthyroidism had no detrimental effects on the renal function.

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