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Association of Thyroid Hormones, Iodothyronine and Deiodinase-1 with Insulin Resistance in Iraqi Adults

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Abstract

Background Iodothyronine deiodinase enzymes have recently gained attention with thyroid hormones (TH) to play a role in many physiological conditions, one of which is insulin resistance (IR).

Objective To investigate the association between TH and serum iodothyronine deiodinase-1 (DIOS-1) levels in participants with and without IR.

Methods A cross-sectional study included 120 Iraqi individuals (male and female) with different body mass index (normal weight, over weight and obese) in the age range between (18-60) years old. Fasting serum levels of insulin, thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) and DIOS-1 were determined by using enzyme-linked immunosorbent assay techniques.

Results Among the 120 subjects, IR found in 25 (20.8%) and 95 (79.2 %) were non-IR. A significant increase in insulin levels was observed in group with IR (27.78±2.77 µIU/ml) compared to non-IR individuals (3.84±0.22 µIU/ml) ($p < 0.001$). There were no significant differences between IR and and non-IR groups in the mean serum levels of (TSH, T3 ,T4, and DIOS-1) 1.33±0.11 µIU/ml, 10.54±0.77 ng/ml, 137.9±6.41 ng/ml and 29.59±1.44 pg/ml, respectively, while those with IR were 1.42±0.21 µIU/ml, 10.67±1.07 ng/ml, 148±12.07 ng/ml and 27.84±1.09 pg/ml, respectively. However, a significant negative correlation between serum level of DIOS-1 and the insulin was found in IR group ($r = -0.425$, $p= 0.034$).

Conclusion This study did not show a relationship between the DIOS-1 enzyme and insulin resistance.

Keywords Iodothyronine deiodinase-1, T3, T4, TSH, insulin resistance.

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List of abbreviations: DIOS-1 = Iodothyronine deiodinase-1, ELISA = Enzyme-linked immunosorbent assay, GLUT4 = Glucose transporter type 4, HOMA-IR = Homeostatic model assessment of insulin resistance, IR = Insulin resistance, T3 = Triiodothyronine, T4 = Thyroxine, TH = Thyroid hormones, TSH = Thyroid stimulating hormone

Introduction

Insulin resistance (IR) is identified as the impaired biological response of target tissues to insulin stimulation. All tissues with insulin receptors can become IR, but the tissues primarily drive IR are the liver, skeletal muscle, and adipose tissue. IR impairs glucose disposal, resulting in a compensatory increase in β-cell insulin production and hyperinsulinemia. Progression of IR can lead to metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes [1,2]. Two hormones secreted from the thyroid gland,

triiodothyronine (T3), and thyroxine (T4), can affect almost all cells in the body and basal metabolism. The secretion of these thyroid hormones (TH) is controlled by the thyroid-stimulating hormone (TSH) secreting from the pituitary gland and they affect glucose metabolism by modulating several pathways in various organs like pancreas, adipose tissue, and liver [3].

Deiodinases are able to remove an iodine atom from the outer or inner ring of the tyrosyl backbone. There are three types of deiodinases, type 1, type 2, and type 3. They are differentially expressed in tissues and have different functions in thyroid hormone deiodination. Deiodinases are important for determining intracellular thyroid hormone availability. Type 1 deiodinase (DIOS-1) is expressed in the liver, kidney, thyroid, and pituitary, it catalyzes outer and inner ring deiodination of T4, T3, and reverse T3 (rT3), and, thus, can both activate and inactivate TH [4]. The main DIOS-1 role is to provide T3 for the circulatory system. Another important function of DIOS-1 is regaining iodide in peripheral tissues [5].

Numerous studies found that IR, diabetes, or metabolic syndrome have associated thyroid dysfunction [6]. These conditions which suppress DIOS-1, causing a decrease in T4 to T3 conversion in the rest of the body, this results in low intracellular T3 levels with subsequent hypothyroid symptoms. Additionally, there is a stimulation type III deiodinase (DIOS-3), which results in an increased conversion of T4 to reverse T3 this increase in reverse T3 further suppresses T4 to T3 conversion and blocks the T3 receptor, worsening hypothyroid symptoms [7]. Therefore, this study aims to investigate the association of serum levels of DIOS-1 with thyroid hormones (T3, T4, and TSH) in Iraqi individuals with IR vs. individuals without IR.

Methods

Study design

A cross- sectional study included 120 Iraqi individuals (males and females) in the age range between (18-60) years old were included.

Sample collection

Five ml of venous blood were withdrawn from fasting participants (at least 8 hours fasting) in aseptic conditions using sterile simple tubes. It usually takes 10-20 minutes for the blood to clot when it is left undisturbed at room temperature (25-28°C).

The serum was obtained by centrifugation for 20 min at 3000 rpm, divided into small aliquots and kept frozen at -20°C until subsequent analysis.

IR was measured by homeostasis model assessment HOMA-IR by the equation (Fasting blood glucose (mg/dL) * Fasting insulin ((µIU/ml)/ 405) [8]. Clinical parameters in this study were determined by different types of enzyme-linked immunosorbent assay (ELISA) techniques.

Fasting serum insulin, DIOS-1 and TSH levels were measured by using sandwich enzyme immunoassay method, while fasting serum T3 and T4 levels were measured by using competitive inhibition enzyme immunoassay. Fasting serum glucose was estimated by Spectrophotometer/Microplate reader.

Statistical analysis

Data were collected, summarized, analyzed and presented using statistical package for social sciences (SPSS) version 26 and Microsoft Office Excel 2019. Most of data were quantitative (numeric) variables and expressed as mean and standard deviation (SD), while only sex was categorical and expressed as number and percentage. Comparison of variables between two groups was done by using unpaired t-test, while between more than two groups was done using analysis of variance (ANOVA) and post hoc Tukey test. Pearson correlation was done to show correlation between variable and expressed as (r) (correlation coefficient) and its P value. The level of significance was considered at P value of equal or less than 0.05.

Results

Table (1) presents the demographic characteristics of the study population. The study participants' mean age was 45±10.29 years while its median was 30 years. There were 56 (47.0%) male participants in the study and 64 (53.0%) female participants comprised the study's participant population.

Table 1. Demographic data of cases

Parameter			Value
Age (yr)	Mean ± SD		45±10.29
	Median (Range)		30 (18-55)
Sex	Male	N (%)	56 (47.0)
	Female	N (%)	64 (53.0)

The study participants' general characteristics are displayed in table (2), among the 120 subjects, 25 (20.8%) were categorized IR group and 95 (79.2%) characterized as non- non-IR group. The IR group had a significantly higher insulin level than the non-IR group (p <0.001). Age differences between the IR and non-IR groups were not statistically significant (p = 0.153). The mean serum differences of (TSH, T3, T4 and DIOS-1) levels between the two groups were not statistically significant.

Table 2. Comparison of parameters between IR and non-IR groups by unpaired t-test

Parameter	IR N=25 Mean±SE	Non-IR N=95 Mean±SE	P value
Age (yr)	29.76±1.75	33.07±1.09	0.153
TSH (µIU/ml)	1.42±0.21	1.33±0.11	0.729
T3 (ng/ml)	10.67±1.07	10.54±0.77	0.920
T4 (ng/ml)	148±12.07	137.9±6.41	0.470
DIOS1 (pg/ml)	27.84±1.09	29.59±1.44	0.543

In this study, the mean age in female subjects was 32.78±1.46 years, in male subjects the mean age was 33.41±1.65 years, which was higher than that of female subjects in non-IR individuals, but these differences were not statistically significant (p = 0.776). In group with IR the mean age of female participants was 29.69±2.45 years; in male participants was 29.83±2.63 years. The differences between male and female were not statistically significant (p=0.969). When we compared the study's various parameters based on the participants' sex as shown in table (3) in both groups. The differences of clinical parameters (TSH, T3, T4, and DIOS-1) between non-IR and IR groups, were not statistically significant based on the p-values provided).

As seen by the findings in table (4), there was no significant correlation between DIOS-1 with TSH and TH in both study groups.

Table 3. Comparison of parameters according to sex in both groups (IR and non-IR) by unpaired t-test

Parameter	Sex	IR Mean±SE	P value	Non-IR Mean±SE	P value
Age (yr)	Male	33.41±1.65	0.776	29.83±2.63	0.969
	Female	32.78±1.46		29.69±2.45	
TSH (µIU/ml)	Male	1.55±0.2	0.078	1.2±0.29	0.323
	Female	1.14±0.12		1.62±0.29	
T3 (ng/ml)	Male	9.97±1.2	0.498	9.55±1.27	0.323
	Female	11.03±1		11.7±1.68	
T4 (ng/ml)	Male	146.29±9.35	0.226	150.64±14.07	0.839
	Female	130.65±8.76		145.57±19.8	
DIOS1 (pg/ml)	Male	28.28±0.77		27.47±1.77	
	Female	30.71±2.6	0.402	28.18±1.36	0.752
	Female	80.04±1.22		76.1±1.46	

Male number=44 and female number=51 in non-IR, while Male number=12 and female number=13 in IR group

Table 4. Correlation of DIOS-1 with other parameters in IR and non-IR groups

Parameter		Non-IR N=95	IR N=25
TSH (µIU/ml)	r	-0.187	-0.013
	p	0.069	0.951
T3 (ng/ml)	r	0.083	0.263
	p	0.422	0.204
T4 (ng/ml)	r	-0.007	0.172
	p	0.950	0.411
	p	0.621	0.714

In the receiver operating characteristic (ROC) curve; according to the area under the curve (AUC), sensitivity and specificity for serum (TSH, T3, T4, DIOS1 levels), indicating that it is a poor discriminator between individuals with IR vs. individuals without IR. These results are given in table (5), figures (1, 2, 3 and 4), respectively.

Table 5. ROC parameters for TSH, T3, T4, and DIOS-1 for discrimination between IR and non-IR groups

Parameter	AUC	P value	Sensitivity	Specificity	Cutoff value
TSH (µIU/ml)	0.536	0.581	48.0%	61.1%	1.27
T3 (ng/ml)	0.501	0.992	51.6%	56.0%	10.65
T4 (ng/ml)	0.563	0.334	56.0%	56.8%	148.75
DIOS-1(pg/ml)	0.519	0.769	49.5%	52.0%	28.25

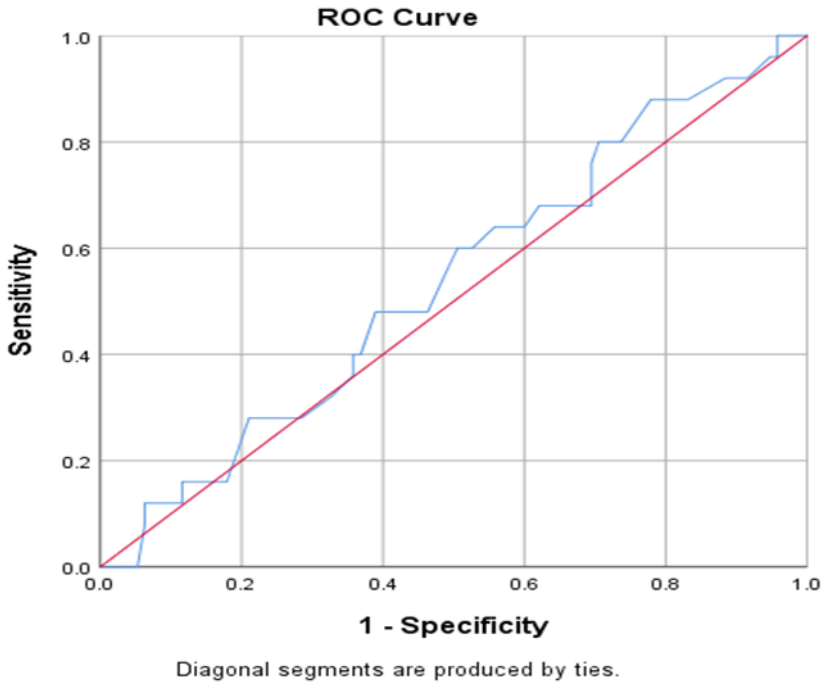

Figure 1. ROC curve for TSH for discrimination between IR and non-IR groups

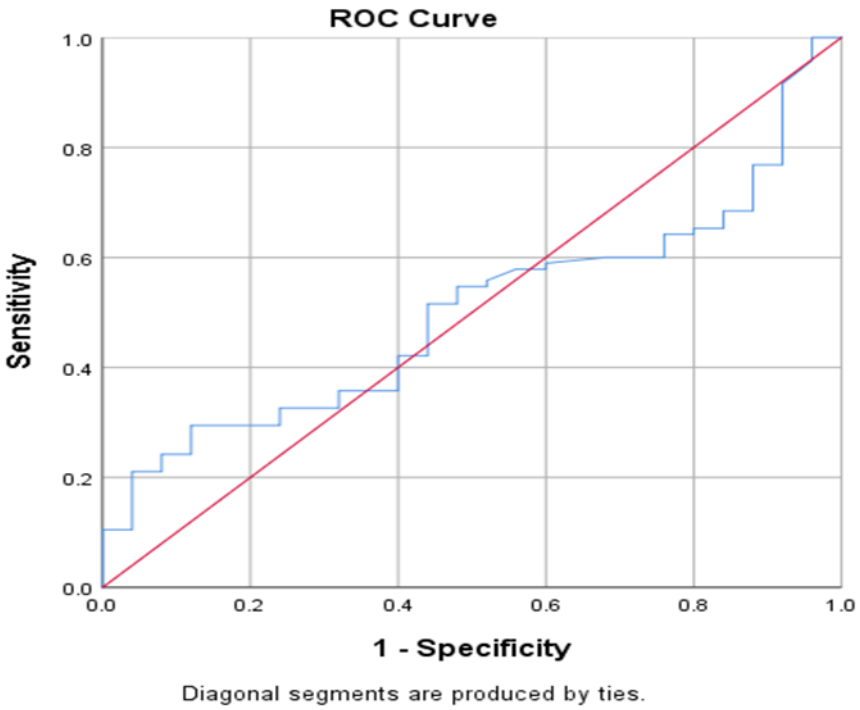

Figure 2. ROC curve for T3 for discrimination between IR and non-IR groups

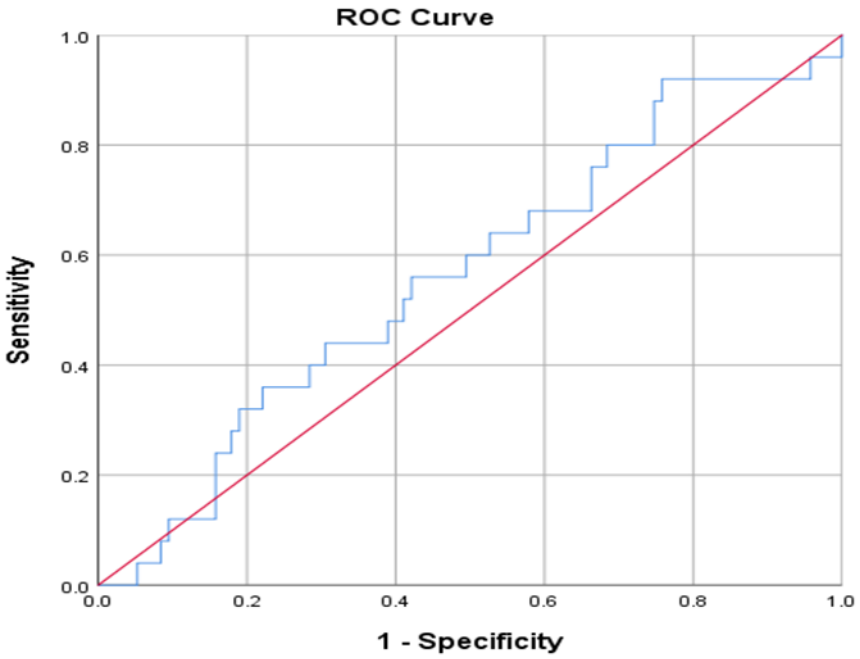

Figure 3. ROC curve for discrimination between IR and non-IR groups

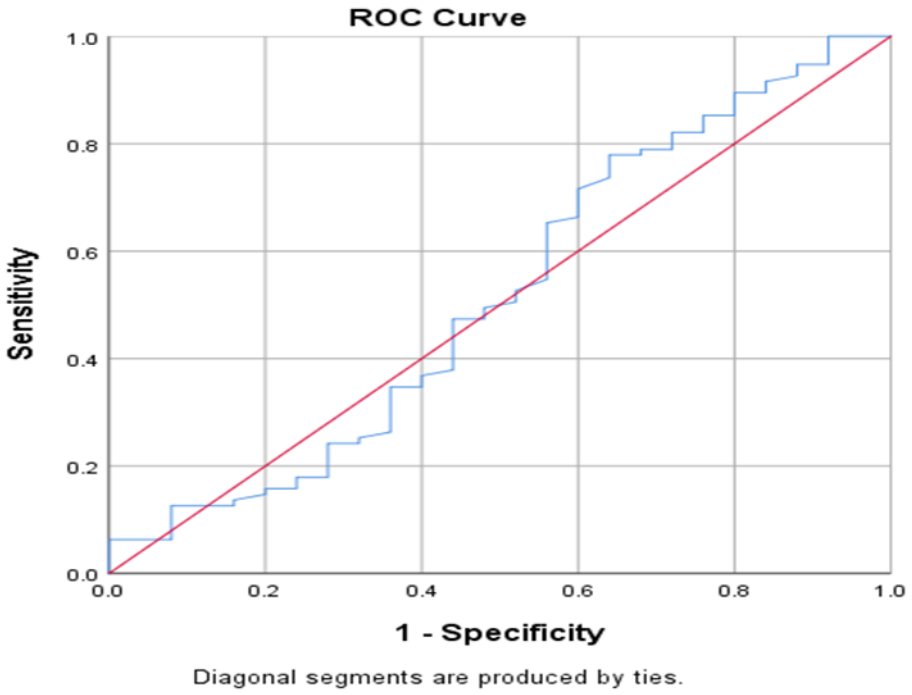

Figure 4. ROC curve for DIOS1 for discrimination between IR and non-IR groups

Discussion

DIOS-1 is the primary deiodinase enzyme that is responsible for converting inactive T4 into active T3 throughout the body. T3 affects glucose metabolism by enhancing glucose uptake into cells and promoting glycolysis (the breakdown of glucose). It can increase insulin sensitivity in some tissues, helping to facilitate glucose uptake [9]. In the current study, DIOS-1 was inversely correlated with insulin level in individuals with IR. This result is in agreement with a number of studies, that found the thyroid hormones, mainly T3 and T4, play a crucial role in regulating metabolism. When thyroid function is compromised, such as in hypothyroidism, the reduced levels of TH can lead to a slowdown in metabolism. This decreased metabolic rate can result in reduced insulin sensitivity and impaired glucose utilization, leading to IR [7,10,11]. Additionally, TH also play a role in the regulation of GLUT4 expression and translocation. In hypothyroidism, there is a decrease in GLUT4 expression and impaired translocation of GLUT4 transporters to the cell membrane in response to insulin stimulation. This results in reduced insulin-mediated glucose uptake in insulin-sensitive tissues, contributing to IR [12,13].

Polymorphisms in the DIOS1 gene can lead to variations in the activity or expression of the DIOS1 enzyme. These genetic variations may influence the conversion of T4 to T3 and subsequently affect the levels of circulating T3. As a result, thyroid function is considered to affect the growth hormone (GH)–insulin-like growth factor (IGF1) axis since T4 stimulates IGF-1 activity in animals in the absence of GH. On the other hand, GH replacement therapy results in an increase in serum T3 and a decrease in T4 and rT3 levels, suggesting a stimulation of DIOS-1 activity [14,15]. IGF-1–related end points, such as body height and skeletal muscle mass; skeletal muscle is an important organ for insulin-stimulated glucose uptake and a lower relative muscle mass was associated with insulin resistance [16,17]. However, the exact nature of the relationship between DIOS-1 and insulin in the context of insulin resistance is still a subject of ongoing research. It's important to note that these

correlations do not necessarily imply causation, and more research is needed to fully understand these complex relationships.

A major limitation to this study was low sample size; the number of participants with IR was very low. Therefore, increasing the sample size with more participants with insulin resistance could give a much clear picture.

In conclusion, the results of this study did not show a relationship between the DIOS-1 enzyme and insulin resistance.

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Author contribution

Al-Saffar: Data collection, experimental work, writing the manuscript draft. Dr. Al-Rubayee: Study design, supervision of the experimental work. Dr. Ali: providing patients samples. All authors were contributed in the final revision of the manuscript.

Conflict of interest

The authors declare that there was no conflict of interest regarding the publication of this paper.

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