

## **Investigation on the Insulin Hormone and Its Receptor in Obesity and type 2 Diabetes Disease**

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### **Abstract**

Obesity is a medical disorder in which excess fat builds up to the point that it has negative health consequences. Type 2 diabetes mellitus (T2DM) is a type of diabetes characterized by a high level of glucose in the blood and the presence of insulin resistance. Here the pancreas suffers from a lack of secretion of the insulin hormone or there is an imbalance in the response to it by the cells. Obesity and T2DM are the most common diseases in Iraq and the world.

The aim of this study is evaluate Insulin and insulin receptor (INSR), in two disease of adult's patients with T2DM and obesity. A total of 60 patients with type 2 diabetes and 60 years old with good health between the ages of (33-57). The patient with T2DM group was divided into a two groups: (Group) (30) obese and (30) non-obese and the control also was divided in two groups: (Group) (30) obese and (30) on obese. The levels of insulin serum, INSR, FBS, HbA1c and lipid profile were measured and then a statistical analysis of the outcome data was performed. The obtained results indicated a significant decrease in the level of insulin and insulin receptor in T2DM patients compared to the control group values also showed decrease in the patients with obesity compared to normal weight group but it was no significant. There was a significant increase in FBS, HbA1c and IR in the patients with T2DM compared to control group, and in the patients with obesity the FBS was significant increase compared to control group and HbA1c showed significant increase in obese patients with T2DM compared to normal weight controls group but in the obese patient without T2DM showed no significant increase, also IR showed no significant in both groups of obese patients compared to normal weight group. The results also revealed an increase in levels of (TC, TG, HDL, LDL, VLDL) in T2DM patients compared to control groups values also showed increase in the levels of (TC, TG, LDL, VLDL) in obese patients with T2DM compared to normal weight with T2DM, only HDL showed decrease and in the obese patients without T2DM compared to control also showed increase in TC, TG, VLDL, but decrease in the levels of HDL and LDL. A conclusion from this study is that

there is a highly action between insulin hormone and its receptor with T2DM in presence the obesity disease.

**Key word:** Type 2 diabetes, obesity, insulin, insulin receptor, insulin resistance.

## 1.Introduction

Obesity is a common disease characterized by an increase in the accumulation of fat in the body, due to an imbalance in food intake between the intake and the consumer(1),(2). A person is considered obese when the body mass index (BMI) is  $30 \text{ Kg/m}^2$  or more(3). Obesity has been related to the development of cardiovascular disease disorders, such as type 2 diabetes mellitus(T2DM), hypertension, heart disease hyperlipidemia, insulin resistance(IR), and cancer(4),(5),(6). Type 2 diabetes mellitus is one of the most severe public health crises of the twenty first century. There are reportedly 415 million people living with diabetes worldwide, with 318 million more having reduced glucose tolerance, putting them at a higher risk of contracting the disease. Provided by 2040, 642 million people will live with this illness(7). T2DM known as non-insulin dependent mellitus or sometimes called adult onset diabetes. In this type the body can produce insulin, but it is not sufficient either or the body is unable to adapt (as well defined as insulin resistance) to its effects, leading to glucose build-up throughout the blood(8). The insulin resistance (IR) can be defined as a decrease in the metabolic response of a cell membrane to insulin hormone in the cells that depended on insulin hormone included muscle, liver and adipose, and don't normal respond to the concentration of insulin hormone(9). IR induces reduced glucose absorption by peripheral tissues. IR and T2DM are caused by changes in many tissues(10),(11). The majority of T2DM patients, though not all, are obese or overweight. IR is a side effect of being overweight(8). People with IR have been found to have decreased insulin receptor (INSR) expression(12). INSR is a glycoprotein that spans the membrane and is required for insulin action, it component from two subunits of extracellular (alpha subunit), which linking insulin, and two membrane-spanning (beta) subunits(13),(14),(9). Some previous studies showed a decrease in the level of insulin and insulin receptors, any defect in insulin receptors has a role in causing IR and T2DM(15). The risk of developing T2DM increases with several factors such as obesity, age, or lack of exercise or patients with hypertension and women with previous gestational diabetes are more likely to develop(8). Also patients with type 2 diabetes have a much higher risk of cerebrovascular morbidity,

cardiovascular and mortality(16). The aim of this study was to evaluate the action of insulin hormone and insulin receptor in obesity and T2DM patients.

## **2. Material and methods**

### **2.1. Subjects**

The study included one hundred and twenty subjects from adults with age range between (33-57) years. Sixty healthy individuals as control group, the control was divided in two groups: (Group) (30) obese and (30) non-obese. Sixty patients with T2DM, the patient group was divided into a two groups: (Group) (30) obese and (30) non-obese. Patients have been diagnosed by specialist physicians at the National Center for Diabetes, based on clinical laboratory tests (immunological and biochemical tests)

Both patient and control groups were free from any visible anomalies and chronic diseases.

### **2.2. Sample collection**

For each person, 5 ml of blood was extracted by used disposable syringes, via a vein puncture and collected in a gel tube. after an overnight fasting, blood samples were obtained during 8:00-11:00 am. Following collected, the blood sample was centrifuged for 10 minutes at 1400 xg. Until the period of study, the resultant serum was preserved at -20 ° C.

### **2.3. Sample analysis**

The body mass index was measured of the subjects studied using the equation:  $BMI = \text{Weight (kilograms)} / \text{Height (meters)}^2$  (17). In addition, the Waist-Height ratio (WHtR) was calculated using the equation:  $WHtR = \text{waist(cm)} / \text{height(cm)}$  (18). Serum insulin hormone and insulin receptors were calculated by Sandwich-ELISA method using the Kits (SunLong/China). Glucose is determined according to the Trinder method following the instructions BIOLABO/France kits(19). HbA1c was estimated by dependent the instructions for Bio-Rad /USA. The lipid profile levels (triglycerides (TC), total cholesterol (TC) and HDL), were estimated using the colorimetric test by dependent the instructions BIOLABO/France kits. LDL and VLDL levels were determined as per the Friedewald equation(20).

## 2.4. Statistical analysis

The study's statistical effects, were calculated by The SPSS version 26 ANOVA statistical software was used to measure, which included the standard deviation, p values and mean, Pearson's correlation as well as the T test. the statistical analyses were significant at  $p < 0.05$  and highly significant at  $p < 0.01$  95% confidence interval

## 3. Results and discussion

All parameter data obtained for T2DM patients and the control group are summarized in two Table 1 and 3. The results revealed that there was a significant difference of the body mass index(BMI) in the obese with T2DM (OT2D) group compared to obese control (OC) ( $P=0.048$ ), but the normal weight with T2DM (NWT2D) showed no significant compared to normal weight control group (NWC) and other previous studies that showed that there is a significant difference of an BMI for T2DM patients(21),(22).

**Table 1: Levels of biochemical parameters in type 2 diabetes disease**

Parameters	OT2D Mean±SD	OC Mean±SD	P value	NWT2D Mean±SD	NWC Mean±SD	P value
BMI (Kg/m <sup>2</sup> )	32.18857 ±1.820659	33.13876 ±1.785520	0.048 <sup>*</sup>	22.84093 ±1.625000	22.68653 ±2.081315	0.75NS
WHtR	0.59627 ±0.029622	0.59535 ±0.048891	0.93NS	0.50590 ±0.034122	0.48230 ±0.0040862	0.018 <sup>*</sup>
FBS(mg/dl)	200.3661 ±59.29150	97.4733 ±7.85217	0.0001 <sup>**</sup>	162.3333 ±44.09968	89.5450 ±9.22499	0.0001 <sup>**</sup>
HbA1c%	8.543 ±1.3622	5.553 ±0.4041	0.0001 <sup>**</sup>	7.413 ±1.0536	5.520 ±0.3458	0.0001 <sup>**</sup>
Insulin(mU/L)	1.1015 ±0.432	2.0769 ±1.32389	0.001 <sup>*</sup>	1.1512 ±0.37946	1.6338 ±0.64388	0.005 <sup>**</sup>
INSR(ng/ml)	1.5026 ±0.36728	1.8296 ±0.443337	0.023 <sup>*</sup>	1.5442 ±0.34175	1.8338 ±0.69272	0.87NS
IR	0.5585 ±0.28214	0.3600 ±0.15811	0.029 <sup>*</sup>	0.4585 ±0.15520	0.3315 ±0.13680	0.017 <sup>*</sup>

(OT2D): Obese type 2 diabetes, (NWT2D): Normal weight type 2 diabetes, (OC): Obese controls, (NWC): Normal weight controls, (INSR): Insulin receptor, (IR): Insulin resistance, (BMI): Body mass index, (WHtR): Waist-Height ratio.

(\*): Significant  $P < 0.05$ , (\*\*) Highly significant  $P < 0.01$

In addition to that, a Waist-Height ratio (WHtR) of the OT2D group showed a no significant difference compared to OC, unlike a NWT2D group that showed a significant increase ( $P=0.018$ ) compared to NWC. A study by Suhayla, et al which showed that there is a significant effect of WHtR for T2DM patients(23). Also, this study revealed that there was a significant increase in fasting blood glucose, HbA1c and IR in T2DM patients compared to the control group. The Tables 1 shows the mean  $\pm$  SD of FBS, HbA1c and IR for OT2D group it was ( $200.3661 \pm 59.29150$  mg/dl,  $8.543 \pm 1.3622$  %,  $0.5585 \pm 0.28214$ ) compared to the obese control OC group it was ( $97.4733 \pm 7.85217$  mg/dl,  $5.553 \pm 0.4041$ %,  $0.3600 \pm 0.15811$ ) and the mean  $\pm$  SD of the NWT2D group it was ( $162.3333 \pm 44.09968$  mg/dl,  $7.413 \pm 1.0536$ %,  $0.4585 \pm 0.15520$ ) compared to the NWC was ( $89.5450 \pm 9.22499$  mg/dl,  $5.520 \pm 0.3458$ %,  $0.3315 \pm 0.13680$ ) and these results are consistent with the results of other previous studies, which showed that T2DM patients suffer from high blood glucose levels, HbA1c, in addition to an increase in insulin resistance(23),(21). The data in Table 1 illustrate the levels of both insulin and insulin receptor that were studied in the T2DM group and the control group. Serum insulin for OT2D and NWT2D were significant decrease ( $P=0.001$ ,  $P=0.005$ ) compared to OC and NWT2D also the INSR showed significant decrease in the OT2D ( $P=0.023$ ) but in NWT2D show no significant ( $P=0.87$ ). The results of this study showed a decrease in insulin levels and INSR in T2DM patients compared to controls where we observed the mean  $\pm$  SD of insulin and INSR for T2DM ( $1.1015 \pm 0.432$  mU/L,  $1.5026 \pm 0.36728$  ng/ml) compared to OC ( $2.0769 \pm 1.32389$  mU/L,  $1.8296 \pm 0.443337$  ng/ml) also the mean  $\pm$  SD for the NWT2D was ( $1.1512 \pm 0.37946$  mU/L,  $1.5442 \pm 0.34175$  ng/ml) compared to NWC ( $1.6338 \pm 0.64388$  mU/L,  $1.8338 \pm 0.69272$  ng/ml) and these results are consistent with some other previous studies that revealed a decrease in the level of insulin and the number of insulin receptors in T2DM patients(15). Also some previous study showed increase in the insulin levels in T2DM patients compared to controls groups(21),(23).

The following Tables 2 and 4 explain the biochemical parameters in obesity disease.

**Table 2: Levels of biochemical parameters in obesity disease**

Parameters	OT2D Mean±SD	NWT2D Mean±SD	P value	OC Mean±SD	NWC Mean±SD	P value
BMI (Kg/m <sup>2</sup> )	32.18857 ±1.820659	22.84093 ±1.625000	0.0001 <sup>**</sup>	33.13876 ±1.785520	22.68653 ±2.081315	0.0001 <sup>*</sup>
WHtR	0.59627 ±0.029622	0.50590 ±0.034122	0.0001 <sup>**</sup>	0.59535 ±0.048891	0.48230 ±0.0040862	0.0001 <sup>**</sup>
FBS(mg/dl)	200.3661 ±59.29150	162.3333 ±44.09968	0.007 <sup>**</sup>	97.4733 ±7.85217	89.5450 ±9.22499	0.001 <sup>**</sup>
HbA1c%	8.543 ±1.3622	7.413 ±1.0536	0.01 <sup>*</sup>	5.553 ±0.4041	5.520 ±0.3458	0.733NS
Insulin(mU/L)	1.1015 ±0.432	1.1512 ±0.37946	0.662NS	2.0769 ±1.32389	1.6338 ±0.64388	0.289NS
INSR(ng/ml)	1.5026 ±0.36728	1.5442 ±0.34175	0.704NS	1.8296 ±0.443337	1.8338 ±0.69272	0.976NS
IR	0.5585 ±0.28214	0.4585 ±0.15520	0.120NS	0.3600 ±0.15811	0.3315 ±0.13680	0.634NS

(OT2D): Obese type 2 diabetes, (NWT2D): Normal weight type 2 diabetes, (OC): Obese controls, (NWC): Normal weight controls, (INSR): Insulin receptor, (IR): Insulin resistance, (BMI): Body mass index, (WHtR): Waist-Height ratio.

(\*): Significant  $P < 0.05$ , (\*\*) Highly significant  $P < 0.01$

Through the data included in a Table 2, we notice a significant increase in BMI ( $P=0.0001$ ) and a WHtR ( $P=0.0001$ ) in patients with obesity, our comparison with a normal weight group, and this is in agreement with other previous studies(24),(25),(22). In addition to that, we notice a significant increase in FBS in obese patients compared to the normal weight group, as well as a significant increase in the level HbA1c in OT2D ( $P=0.01$ ) compared with NWT2D as for OC, it appeared to be no significant ( $P=0.733$ ) compared to NWC, and this is consistent with the results of previous studies, showed increase in the HbA1c in the obese patients with T2DM (24),(25). As for all IR, INSR and insulin, they are no significant in obese patients compared to normal

weight groups unlike the study by Amr et al, it showed a significant increase in insulin level and IR in the patients with obesity and T2DM(24).

**Table 3: Levels of Lipid profile in type 2 diabetes disease**

Parameters	OT2D Mean±SD	OC Mean±SD	P value	NWT2D Mean±SD	NWC Mean±SD	P value
TC(mg/dl)	234.933 ±26.8802	170.450 ±26.5545	0.0001**	194.233 ±21.0200	167.217 ±23.8388	0.0001**
TG(mg/dl)	224.233 ±57.6910	125.947 ±59.3757	0.0001**	160.667 ±40.5236	82.633 ±31.2061	0.0001**
HDL(mg/dl)	44.033 ±4.3903	38.986 ±9.4902	0.011*	48.500 ± 5.7401	42.773 ±10.5525	0.011*
LDL(mg/dl)	146.487 ±26.2778	104.824 ±24.2543	0.0001**	113.600 ±21.6552	107.916 ±29.8121	0.42NS
VLDL(mg/dl)	44.847 ±11.5382	25.189 ±11.8751	0.0001**	32.133 ± 8.1047	16.527 ± 6.2412	0.0001**

TG: Triglyceride, TC: Total Cholesterol, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, VLDL: Very Low Density Lipoprotein, (OT2D): Obese type 2 diabetes, (NWT2D): Normal weight type 2 diabetes, (OC): Obese controls, (NWC): Normal weight controls.

(\*): Significant  $P < 0.05$ , (\*\*) Highly significant  $P < 0.01$ , NS: No significant

The results of the lipid analysis to T2DM patients and controls are summarized in Table 3. Where TC, TG, HDL, VLDL showed a significant increase ( $p < 0.01$ ) in the OT2D compared to the OC and NWT2D compared to NWC group. The mean±SD of (TC,TG,HDL,VLDL) for OT2D (234.933±26.8802 mg/dl, 224.233±57.6910 mg/dl, 44.033±4.3903 mg/dl, 44.847±11.5382 mg/dl) compared to OC (170.450±26.5545 mg/dl, 125.947±59.3757mg/dl, 38.986±9.4902 mg/dl, 25.189±11.8751mg/dl) also the mean±SD for NWT2D was (194.233±21.0200 mg/dl, 160.667±40.5236 mg/dl, 48.500± 5.7401 mg/dl, 32.133± 8.1047 mg/dl) compared to NWC (167.217±23.8388 mg/dl, 82.633±31.2061 mg/dl, 42.773±10.5525 mg/dl, 16.527± 6.2412 mg/dl) and these presented results are consistent with previous studies that showed an increase in levels (TC,TG,VLDL) in T2DM patients compared to the controls group, but HDL do not agree

with other studies, as previous studies show a decrease in the level of HDL in patients with T2DM compared to the control group (23),(21),(26),(27). In addition, in some other studies, there is an increase in the level of HDL in T2DM patients compared to the control group(24). Also in this study showed significant increase in the levels of low density lipoprotein (LDL) in OT2D compared to OC , but it was no significant in NWT2D compared to NWC,these was consistent with the results of other previous studies that showed an increase in LDL in T2DM compared to the control group (23),(21),(26),(27).

**Table 4: Levels of Lipid profile in obesity disease**

<b>Parameters</b>	<b>OT2D Mean±SD</b>	<b>NWT2D Mean±SD</b>	<b>P value</b>	<b>OC Mean±SD</b>	<b>NWC Mean±SD</b>	<b>P value</b>
TC(mg/dl)	234.933 ±26.8802	194.233 ±21.0200	0.0001**	170.450 ±26.5545	167.217 ±23.8388	0.622NS
TG(mg/dl)	224.233 ±57.6910	160.667 ±40.5236	0.0001**	125.947 ±59.3757	82.633 ±31.2061	0.001**
HDL(mg/dl)	44.033 ±4.3903	48.500 ± 5.7401	0.001**	38.986 ±9.4902	42.773 ±10.5525	0.153NS
LDL(mg/dl)	146.487 ±26.2778	113.600 ±21.6552	0.0001**	104.824 ±24.2543	107.916 ±29.8121	0.661NS
VLDL(mg/dl)	44.847 ±11.5382	32.133 ± 8.1047	0.0001**	25.189 ±11.8751	16.527 ± 6.2412	0.001**

TG: Triglyceride, TC: Total Cholesterol, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, VLDL: Very Low Density Lipoprotein, (OT2D): Obese type 2 diabetes, (NWT2D): Normal weight type 2 diabetes, (OC): Obese controls, (NWC): Normal weight controls.

(\*): Significant  $P < 0.05$ , (\*\*) Highly significant  $P < 0.01$ , NS: No significant

The Table 4 showed highly significant difference ( $p < 0.01$ ) in TC, TG, HDL, LDL and VLDL in OT2D compared to the NWT2D, also showed highly significant increase ( $p < 0.01$ ) in TG and VLDL in OC compared to NWC, but TC, HDL and LDL showed no-significant( $p > 0.05$ ). The mean±SD of TC, TG, LDL and VLDL increase in the OT2D than the NWT2D un like HDL it was high in the NWT2D than the OT2D. Also mean±SD of TC, TG and VLDL was high in the



OC than the NWC, but HDL, LDL was less in the OC than the NWC. These results are consistent with the results of study by Amr et al, who showed that the level of TC, TG and VLDL increase in the obese patients with T2DM and patients and HDL decrease compared with control group(24). Also a previous study showed that the levels of TC, TG and VLDL increase in obese patients compared to normal weight except the HDL decrease in the obese patients compare to control group(28). On the other hand, LDL in OC showed no significant decrease ( $p>0.05$ ) compared to the NWC and this does not coincide with previous studies(24),(28).

To investigate on the relationship between insulin receptor INSR and all parameters, it had applied Pearson's correlation analysis.

**Table 5: Correlation of INSR in sera patients and control groups with other Parameters**

Parameters	OT2D		NWT2D		OC		NWC	
	r	p	r	p	r	p	r	p
<b>Age (years)</b>	-0.359	0.071	0.012	0.952	0.368	0.216	-0.112	0.716
<b>BMI (Kg/m<sup>2</sup>)</b>	-0.288	0.264	0.223	0.274	0.254	0.402	0.286	0.343
<b>WHtR</b>	-0.239	0.240	0.084	0.683	-0.550	0.051	0.286	0.343
<b>FBS (mg/dl)</b>	-0.353	0.077	-0.282	0.163	-0.734	0.004 <sup>**</sup>	0.705	0.007 <sup>**</sup>
<b>HbA1c %</b>	-0.414	0.035 <sup>*</sup>	-0.003	0.988	-0.222	0.465	0.352	0.239
<b>TC (mg/dl)</b>	-0.119	0.564	-0.275	0.174	0.284	0.346	-0.017	0.957
<b>TG (mg/dl)</b>	0.229	0.261	-0.441	0.024 <sup>*</sup>	-0.145	0.636	-0.218	0.475
<b>HDL (mg/dl)</b>	0.126	0.539	0.119	0.563	0.352	0.261	-0.160	0.602
<b>LDL (mg/dl)</b>	-0.246	0.226	-0.134	0.513	0.200	0.513	0.093	0.762
<b>VLDL (mg/dl)</b>	0.229	0.261	-0.441	0.024 <sup>*</sup>	-0.145	0.636	-0.218	0.475
<b>Insulin (mU/L)</b>	0.500	0.009 <sup>**</sup>	0.181	0.376	0.010	0.975	0.480	0.097
<b>IR</b>	0.119	0.564	0.024	0.907	0.011	0.973	0.610	0.027 <sup>*</sup>

(\*): significant  $p<0.05$ , (\*\*): highly significant  $p<0.01$

The results in Table 5 showed that the INSR had a strong negative correlation with FBS ( $r = -0.734$ ) in OC but in NWC group showed a strong positive correlation ( $r = +0.705$ ), moderate negative correlation with HbA1C in OT2D ( $r = -0.414$ ) and with TG, VLDL in NWT2D ( $r = -0.441$ ). While INSR had a strong positive correlation with insulin only in the OT2D ( $r = +0.734$ ). In addition, the results showed that the INSR had a positive correlation with IR ( $r = +0.610$ ) in NWC group.

In other word it could said that the obesity had an impact on the binding of INSR with its hormones, the presence of obese disease in T2DM found a strong (+) relation with insulin, furthermore the relation of INSR with FBS changed from (+) to (-) when the group is obese (changed from NWC to OC).

#### 4. Conclusion

This study indicates a close association between the insulin hormone and insulin receptor in T2DM disease, it could said that the obesity had an impact on the binding of INSR with its hormones, the presence of obese disease in T2DM found a strong (+) relation with insulin, furthermore the relation of INSR with FBS changed from (+) to (-) when the group is obese (changed from NWC to OC).

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