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RESEARCH ARTICLE

COMPARISON OF INSULIN RESISTANCE, PROLACTIN AND HBA1C WITH RELATION TO OBESITY IN MEN AND WOMEN OF HEALTHY CONTROL AND DIABETIC PATIENTS / MEISAN-IRAQ

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ABSTRACT

Even though the scientific community has started unraveling the mysteries of the close linkage between obesity, insulin resistance, hormones and their physiological effects in diabetic patients, a lot still remains to be discovered. In province of Meisan (southern of Iraq), to date, no study has investigated on obesity, insulin resistance and its effects on type 2 diabetic patients. Therefore, this study embarked on to explore the comparison of insulin resistance, prolactin and HbA1c with relation to obesity in men and women of healthy control and diabetic patients in Meisan province (southern of Iraq). A total of 50 consenting normal individuals (25 men, and 25 women) and 50 adult type 2 diabetic patients (26 men, and 24 women) seen in the central laboratory of Al- Sadder General Hospital and Diabetes and Endocrine Center at the province of Meisan, were evaluated in this cross sectional study. Their fasting glucose, fasting insulin, HbA1c, weight, height, BMI and prolactin were evaluated. Also, insulin resistance parameters (HOMA2-IR, HOMA%B and HOMA%S) were calculated using HOMA2 calculator software. We used student t-test and Pearson's correlation coefficient to find the statistical significance. On comparison, levels of serum glucose, insulin, HOMA2-IR, BMI, prolactin were significantly ($p<0.05$) higher as well as level of blood HbA1c ($p<0.01$) in both men and women type 2 diabetes mellitus cases as compared with those of the controls. On the other hand, there was a positive statistically significant correlation was observed between IR and each of BMI, HbA1c and prolactin, respectively in diabetic patients. The results obtained indicated that increased obesity leads to increased insulin resistance which affected on levels of HbA1c and prolactin in men and women type 2 diabetic patients. Our data indicate that these strong associated between insulin resistance and levels of HbA1c and prolactin could be considered as good biomarkers of the risk of T2D and obesity in men and women type 2 diabetic patients.

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INTRODUCTION

Type 2 diabetes is a common condition managed in primary healthcare. Evidence is accumulating that insulin resistance may be the common underlying etiological factor for the individual components of the metabolic syndrome (Alberti and Zimmet, 1998) and for type 2 diabetes. Abdominal obesity is a strongly concluded phenotypic companion for a cluster of metabolic abnormalities characterized by insulin resistance (Groop, 2000). However, the association with abdominal obesity and features of the metabolic syndrome has been reported to vary with gender (Ho *et al.*, 2001), and with different degrees of obesity (Ascaso *et al.*, 2003). Although abdominal obesity is the best obesity-related predictor of type 2 diabetes it is not clear to what extent abdominal obesity can be used as a surrogate measure for insulin resistance in subjects who have already developed type 2 diabetes (Chan *et al.*, 1994). Type 2 diabetes is a common condition managed in primary healthcare. Evidence is accumulating that insulin resistance may be the common underlying etiological factor for the individual components of the metabolic syndrome and for type 2 diabetes. Abdominal obesity is a strongly concluded phenotypic companion for a cluster of metabolic abnormalities characterized by insulin resistance. However, the association with abdominal obesity and features of the metabolic syndrome has been reported to vary with gender, and with different degrees of obesity (Kale and Rawat, 2006). Although abdominal obesity is the best obesity-related predictor of type 2 diabetes it is not clear to what extent abdominal obesity can be used as a surrogate measure for insulin resistance in subjects who have already developed type 2 diabetes (Sindelka *et al.*, 1999). Prolactin (PRL) is a pituitary hormone known to control the initiation and maintenance of lactation. However, as the PRL receptor is expressed in various tissues and cells such as endometrium, the prostate, pancreatic islets, and adipocytes, PRL is also involved in various other physiological functions including metabolism. Experimental studies

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indicated that PRL has effects on food intake, body weight gain, and insulin resistance via inhibiting adiponectin and IL-6 production in adipose tissue (Ben-Jonathan *et al.*, 2008), which may lead to type 2 diabetes mellitus. On the other hand, experimental studies also showed that PRL has effects on growth of pancreatic ß-cells and reduces threshold for glucose-stimulated insulin secretion (Petryk *et al.*, 2000), which indicate that PRL has a protective effect against type 2 diabetes mellitus. These findings suggest that in humans, the effects that PRL induces may be complex or may vary depending on different conditions. Human studies with high serum PRL levels caused by antipsychotic drugs or prolactinoma suggested that increased levels of PRL may have adverse metabolic effects leading to type 2 diabetes (Berinder *et al.*, 2001). However, studies on serum PRL levels within the physiological range showed conflicting results. Some studies found a positive association between serum PRL levels and metabolic parameters such as incident hypertension (Zhang *et al.*, 2010), waist and aortic stiffness as seen in individuals with pathologically high serum PRL levels. Furthermore, bromocriptine, a dopamine agonist that is well known to suppress serum PRL levels, has been shown to effectively improve insulin sensitivity, and has been approved for the treatment for type 2 diabetes mellitus in the United Sates (Lamos *et al.*, 2016). In contrast, other studies have shown an inverse association between serum PRL levels and metabolic parameters such as cardiovascular events, cardiac remodeling (Corona *et al.*, 2011), diabetes, metabolic syndrome, homeostasis model assessment (HOMA) for insulin resistance and adverse lipid profiles (Balbach *et al.*, 2013). Therefore, the association between serum PRL levels and metabolism in subjects with serum PRL levels within the physiological range requires further evaluation. As serum PRL levels are regulated differently between genders, any association between serum PRL levels and any other factors should be evaluated separately for each gender. However, most previous studies have been conducted in either individual gender alone (Corona *et al.*, 2011). Some studies with subjects stratified based on gender did show gender-specific association between serum PRL levels and glucose-induced insulin release, cardiac remodeling and metabolic syndrome (Reis *et al.*, 1997). Even though the scientific community has started unraveling the mysteries of the close linkage between obesity, insulin resistance, hormones and their physiological effects, a lot still remains to be discovered. In the province of Meisan (southern of Iraq), to date, no study has investigated on obesity, insulin resistance and its effects on type 2 diabetic patients. Therefore, this study embarked on to explore the comparison of insulin resistance, prolactin and HbA1c with relation to obesity in men and women of healthy control and diabetic patients in Meisan province (southern of Iraq).

MATERIALS AND METHODS

Subjects

This study was carried out on peoples who suffering from type II of diabetes mellitus in Meisan province. The study samples included (50) patients suffering from type II of diabetes (26 men and 24 women) aged between (37) and (65) years, and controlled with (50) healthy individuals (25 men and 25 women) aged between (36) and (65) years. Standard self-administered questionnaires were used to define age, duration of diabetes, health habits (smoking, alcohol consumption and exercise), medical history and current medications. Individuals should not belong to the class of secondary diabetes due to pancreatic diseases, hormonal abnormalities, drug induced, genetic syndromes and those who used exogenous hormone, opium or medication which might affect sex hormone level were excluded from the study…etc. The control group was health Individuals; not suffering from type-2 diabetes nor having any family history of type-2 diabetes mellitus; not suffering from any acute or chronic cardiovascular diseases; not taking any drug believed to alter plasma glucose level.

Samples

The studied samples of patients were collected from the central laboratory of Al- Sadder General Hospital and Diabetes and Endocrine Center at the province of Meisan. All blood samples were obtained in the morning between 08:00 and 09:00 hours after a 12-h fast and a 30-min of rest in the supine position. Blood samples were collected from the antecubital vein. Rubber tourniquet was applied for less than one minute and the site to be punctured cleaned with 70% methylated spirit. A single blood sample was collected from each subject. About 10ml of blood was taken. About 1ml blood was placed into EDTA vacutainer tube to perform HbA1c for cases and controls. The rest of the blood samples were placed in plain tubes and allowed to clot. After the blood had clotted it was placed in a centrifuge and spun at 402 x g for 10 minutes to obtain the sera. The obtained sera immediately use in detection of variables in this study, and others were stored in deep freezing at (-20ºC) until using.

Methods

Body mass index (BMI)

Body mass index was calculated as weight in kilograms divided by height in meters squared using the following formula:

BMI (kg/m^2) = Wt in kg / Ht in m^2

Height and weight were measured by using a regularly calibrated stadiometer and balance-beam scale with participants wearing light clothing and no shoes.

Measurement of Insulin Resistance Parameters

Insulin resistance parameters (insulin resistance (HOMA2-IR), beta cell activity (HOMA%B) and insulin sensitivity (HOMA%S)) were calculated from fasting insulin and fasting blood glucose (FBG) using HOMA2-R calculator software.

Methods of Biochemical Estimation

The control and diabetic patients (type II) blood samples were analyzed for biochemical parameters by standard procedures as follows: Serum glucose was estimated by kit (Randox /England) (Trinder, 1969), serum insulin was estimated by kit (demeditec / Germany) (Judzewitsch *et al.*, 1982), blood HbA1c was estimated by kit (STANBIO / Germany) (Abraham *et al.*, 1978) and serum prolactin (Human / Germany) (Maddox *et al.*, 1991).

Statistical Analysis

We used student t-test and Pearson's correlation coefficient to find the statistical significance. A p value <0.05 was to be

considered statistically significant and P < 0.01 for highly significant.

RESULTS AND DISCUSSION

In patients where body mass index as a clinical parameter that can be used to determine the extent of glycemic control. Table 1 and Figure 1 were clearly showed that in DM patients group, BMI was found to be significantly (p <0.01) higher in both men and women with compared to controls. On the other hand, a significant differences (P <0.01) were also observed in BMI between the men and women diabetic patients group. Data obtained in the present study, show a significant increase in IR level (3.95 ± 0.57 Vs. 1.36±0.23 and 4.09 ± 59 Vs. 1.18 ±0.13, P < 0.05) respectively, in men and women type 2 diabetic patients compared to control. Also, Insulin/ Glucose ratio was significantly (P < 0.05) higher in men and women type 2 diabetic patients compared to control (0.192 Vs. 0.093 and 0.198 Vs. 0.083, respectively). Furthermore, there was no significant difference between HOMA%B± level of cases and controls. Moreover, level of HOMA%S± was significantly lower in cases compared to controls, as shown in Table 2. Results in Table 3 show that NIDDM patients had higher level of serum glucose level (150 ± 23 Vs. 107 ± 9.52 mg/dl, P < 0.01), insulin hormone level (29.15 ± 5.51 Vs. 9.70 ± 1.59 µU/ml, P < 0.01) and blood HbA1c % level (8.93 ±1.21Vs. 5.89 ± 0.90, P < 0.01). Also, there was a significant increase in prolactin level (24.70 ± 4.08 Vs. 12.74 ± 3.22; and 31.22 ±5.49 Vs. 14.22 ± 2.91 ng/ml, P < 0.01), respectively in men and women type 2 diabetic patients compared with those of control. The results confirmed that insulin resistance was positively and highly significantly correlated with BMI (r = 0.701; 0.716, P<0.01) and Prolactin (r = 0.559; 0.543, P < 0.01) in men and women NIDDM patients, respectively. Also, there was a highly significantly correlated with $HbA1_C$ (r = 0.713, P < 0.01) in NIDDM patients, as shown in Table 4 and Figures 2, 3 and 4. Obesity probably act as a diabetogenic factor, through increasing resistance to the action of insulin, in those genetically predisposed to develop type 2 diabetes; insulin resistance lead to higher plasma levels of insulin, which cause an increase in appetite, so people eat more and put on weight (Edwards *et al.*, 1991). In the present study it was observed that DM patients presented with significantly higher BMI values compared to controls and there is no significant difference between BMI values of both patients groups. This constitutes to the notion that obesity may be one of the etiological factors in the development of DM, and mostly as a result of loss of early-phase insulin secretion in response to glucose which occurs relatively early in the development of type 2 DM (Ward *et al.*, 1984).

This loss is critically important as the early burst of insulin secretion plays an important role in priming target tissues of insulin, especially the liver responsible for normal glucose homeostasis following food uptake; and mealtime glucose excursion (spikes) occur when this process was impaired (Bruttomesso *et al.*, 1999). The relation between obesity and diabetes was investigated in many studies (Knowler *et al.*, 1981) which is showed that obesity is one of the modifiable cardiovascular risk factor that is far more prevalent in those individuals with type 2 DM than in the general population (Perry *et al.*, 1995). Also, reported that obesity and physical inactivity are important independent risk factors for type 2 middle aged men. This result may be due to the mammalian adipose tissues consist of white and brown adipose. The brown fat is involved in thermogenesis and in human it is mainly found in newborn infants. Instead, the white adipose tissue has an important role in maintaining whole-body glucose homeostasis as well as lipid metabolism and adipocyte dysfunction is closely linked to insulin resistance and T2D. The white adipose tissue secretes numerous cytokines and hormones collectively known as adipocytokines, or adipokines (Ouchi *et al.*, 2011). Most of them are pro-inflammatory, a unique anti-inflammatory and insulin sensitizing property (Yamauchi *et al.*, 2001). This is important because chronic low-grade inflammation has been implicated in obesity and insulin resistance. C-reactive protein (CRP) is an acute-phase protein that serves as an important marker of systemic inflammation and is also related to insulin resistance (Ndumele *et al.*, 2006). Increased lipolysis and decreased triglyceride storage lead to higher circulating levels of non-esterified fatty acids and triglycerides. This causes ectopic lipid accumulation and impairs insulin-stimulated glucose uptake in skeletal muscle, which is believed to be a primary cause of insulin resistance (Guilherme *et al.*, 2008). Similarly, excess fatty acids in the liver decrease the responsiveness of the hepatic cells to insulin. High levels of non-esterified fatty acids may be the most critical determinant of insulin sensitivity. One proposed mechanism is that increased intracellular concentrations of fatty acid metabolites, such as fatty acyl-coenzyme A (fatty acyl-CoA), diacylglycerol (DAG), and ceramides lead to phosphorylation of insulin receptor substrates at serine/threonine site, and this disrupts the insulin signaling pathway by deactivating the phosphatidylinositol 3–kinase (PI 3-kinase) (Shulman, 2000). As a result, downstream insulin signaling and glucose transport is compromised. Fat distribution is another important contributor of insulin resistance and abdominal obesity is closely associated with adverse metabolic consequences (Sandeep *et al.*, 2010), (Hyun *et al.*, 2008). Visceral adipose tissue is more lipolytic and less insulin-sensitive than the subcutaneous adipose tissue (Montague and O'Rahilly, 2000). Together with the fact that the visceral fat depot is in closer proximity to the liver, portal non-esterified fatty acids levels are elevated in abdominal obesity. The expected results are increased hepatic glucose production and peripheral hyperglycemia (Bjorntorp, 1991).

The positive correlation between insulin resistance and HbA1c level may be due to the elevated level of insulin resistance, decreased activity of insulin hormone lead to hyperglycemia which causing increased glycation of hemoglobin and increased release of free iron from glycated proteins like hemoglobin. This makes a vicious cycle of hyperglycemia, glycation of hemoglobin and increase in levels of free iron and ferritin. This increased presence of iron pool will enhance oxidant generation leading damage to biomolecules. Glycated hemoglobin percentage is a valuable and widly used adjunct to blood glucose determination for monitoring long term glycemic control. It is a measure of risk of complications of diabetese. These results go with the result of (Maheshwari *et al.*, 2015). On the other hand, increased accumulation of iron affects insulin synthesis and its secretion from the pancreas and interferes with the insulin-extracting capacity of the liver. Iron deposition in muscle decreases glucose uptake because of muscle damage (Fernandez-Real *et al.*, 2002). Also, this result probably was obtained due to elevation level of insulin resistance in diabetic patients lead to prolactin knockout or prolactin receptor deficiency which is accompanied by β-cell hypoplasia, a reduced pancreatic insulin mRNA level, a blunted insulin secretory response to glucose, and mild glucose

Table 1. Body Mass Index (BMI) in men and women of control and patients with type 2 DM. The values are the Mean ± SD

	Type 2 DM		Healthy control		Significance p-value
	Men	Women	Men	Women	
BMI (kg/m^2)	25.49 ± 1.34	26.51 ± 2.562	21.35 ± 1.54	22.54 ± 2.75	HS

Table 2. Study the Insulin Resistance Parameters. The values are the Mean ± SD

	Type 2 DM		Healthy Control		Significance p-value
Parameters	men	women	men	women	
Glucose (mg/dl)	150 ± 19.21	149 ± 15.30	108± 9.2	106± 8.3	HS
Insulin (µu/ml) ±SD	28.85± 3.77	29.65± 4.06	10.08±1.66	8.81±0.99	S
Insulin/ Glucose	0.192	0.198	0.093	0.083	S
HOMA2IR±SD	3.95 ± 0.57	4.09 ± 0.59	1.36±0.23	1.18 ±0.13	S
HOMA%B±	73.56 ± 2.39	72.10±2.24	75.57±13.1	85.05±9.19	NS
HOMA%S±	25.78 ± 3.90	24.91± 3.70	80.80±12.46	76.20±14.02	S

Table 3. Levels of HOMA2-IR, BMI, glucose, HbA1c, Insulin hormone and prolactin in men and women of control and patients with type 2 DM. The values are the Mean ± SD

		Type 2 DM n = 50					Control n=50	Significance p-value
		Mean ± SD	SE	Range	95 % C.I		Mean ± SD	
					Lower	Upper		
HOMA2-IR	Men	3.95 ± 0.57	0.11	1.98- 3.98	2.8328	5.0672	1.36±0.23	S
	Women	4.09 ± 0.59	0.12	2.11 – 4.24	2.9336	5.2464	1.18 ±0.13	
BMI (kg/m^2)	Men	25.49 ± 1.34	0.26	25.3 -27.52	22.8636	28.1164	21.35± 1.54	HS
	Women	26.51 ± 2.56	0.52	25.7 –27.67	21.4884	31.5315	22.54±2.75	
Glucose (mg/dl)		150 ± 23	3.25	128 – 178	104.92	195.08	107 ± 09	HS
$HbA1_C$%		8.93 ±1.21	0.17	7.1 –11.3	6.5584	11.3016	5.89 ± 0.9	HS
Insulin (µU/ml)		29.15 ± 5.51	0.78	18.96 –35.31	18.3504	39.9496	9.70 ±1.59	HS
Prolactin (ng/ml)	Men	24.70 ± 4.08	0.80	18.43 – 32.20	16.7032	32.6968	12.74 ± 3.22	S
	Women	31.22 ±5.49	0.87	24.50 – 39.70	20.4596	41.9804	14.22 ± 2.91	

Table 4. Correlation coefficient (r) between the insulin resistance and some biochemical Parameters (HbA1c, BMI and prolactin) in patients with type 2 DM. The values are the Mean ± SD

The correlation of insulin resistance *vs.* other variables		Type 2 DM, n = 50	Significance p-value
		Correlation coefficient (r)	
VS. BMI (kg/m^2)	Men	0.701	HS
	Women	0.716	HS
Vs. $HbA1_C$ %	Total Patients	0.713	HS
Vs. PRL (ng/ml)	Men	0.559	HS
	Women	0.543	HS

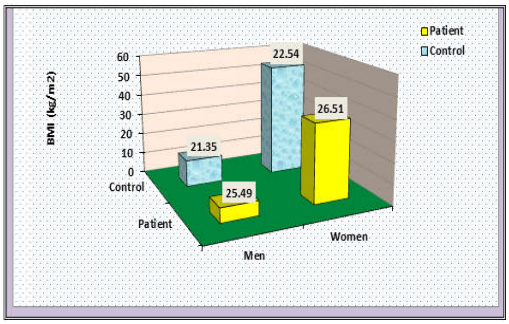

Figure 1. Body Mass Index (BMI) in men and women of control and patients with type 2 DM

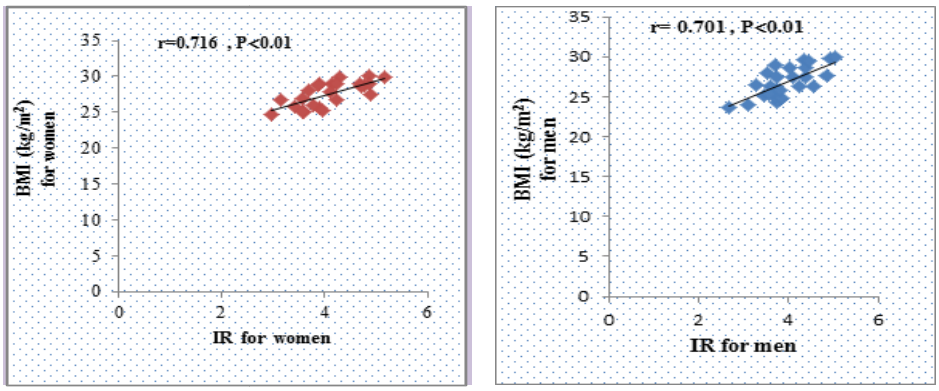

Figure 2. Correlation coefficient (r) of insulin resistance (IR) with Level BMI of NIDDM Patients

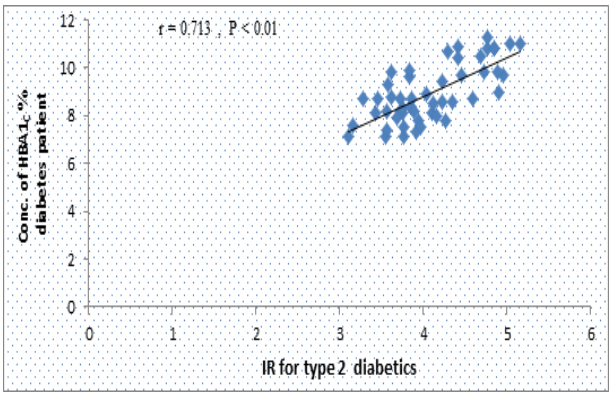

Figure 3. Correlation coefficient (r) of insulin resistance (IR) with Level of $HbA1_C$ % in blood of NIDDM Patients

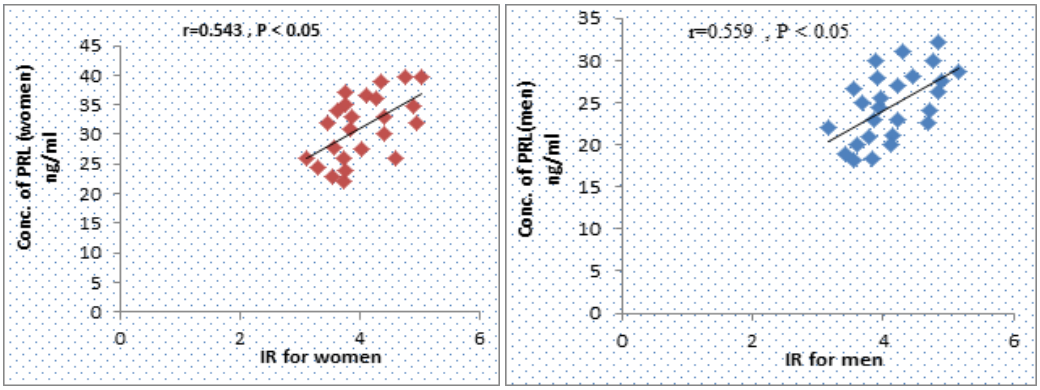

Figure 4. Correlation coefficient (r) of insulin resistance (IR) with Level of Prolactin in serum of NIDDM Patients

intolerance (LaPensee *et al.*, 2006). Furthermore, physiologically elevated prolactin levels induce normal adaptive increases in glucose-stimulated insulin secretion through expanding β-cell mass and improving hepatic insulin sensitivity (Park *et al.*, 2012) and have an indirect action by increasing hypothalamic dopamine synthesis to contribute to the improved energy and glucose homeostasis (Lyons *et al.*, 2012). Moreover, excessive high levels of prolactin exacerbate whole-body and hepatic insulin resistance and impair the insulin secretory capacity in diabetic patients with hyperprolactinemia caused by prolactinoma (Berinder *et al.*, 2011). Patients with pituitary prolactinoma often have a higher risk of hyperglycemia, accompanied by obesity and insulin resistance, and dopamine agonist treatment, such as bromocriptine, is used to reverse these symptoms (Wang *et al.*, 2013). Finally, increased prolactin secretion may occur due to reduced D_2 receptor availability in the brain, which makes these individuals more likely to have elevated prolactin secretion (Pereira-Lima *et al.*, 2013).

Conclusion

From the above study, it can be concluded that increased obesity leads to increased insulin resistance which affected on levels of HbA1c and prolactin in men and women type 2 diabetic patients. Our data indicate that these strong associated between insulin resistance and levels of HbA1c and prolactin could be considered as good biomarkers of the risk of T2D and obesity in men and women type 2 diabetic patients.

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