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Prolactin is a Novel Biochemical Marker in Sera of Iraqi Type-2 Diabetic Women With Metabolic Syndrome in Baghdad.

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Abstract

Metabolic syndrome (MS) is a group of clinical and biological abnormalities included risk of insulin resistance , disorders in glucose metabolism , abdominal obesity and abnormal lipid profile these features confer a greater risk of cardiovascular diseases . Anyway, the co-occurrence of diabetes mellitus and metabolic syndrome potentiates the cardiovascular risk associated with each of the two conditions. The present study aimed to determine a relationship between prolactin level in type -2- diabetic Iraqi women and metabolic syndrome, as well to find a relationship between prolactin level and other studied biochemical markers. seventy menopausal diabetic women with metabolic syndrome with age in range (45-50) years were enrolled in this study , and were compared with matched age control group which consisted of menopausal women suffering from uncomplicated diabetic patients (without metabolic syndrome). Two groups were not given any treatment , they were newly diagnosed. This study highlights the role of metabolic syndrome in the abnormalities of prolactin blood glucose , lipid profile , glycated hemoglobin and body mass index regardless the role of diabetic mellitus. Available evidence from the present study have reported that prolactin is a novel biochemical marker in sera of Iraqi menopausal type-2 diabetic women with metabolic syndrome . Moreover this study is the first highlights not only the association between lower level prolactin and metabolic syndrome in type-2 diabetic women but also the correlation between lower prolactin level and other biochemical markers (Lipid profile , HbA_{1c} and BMI) in type-2- diabetic women with metabolic syndrome .

Keywords : Prolactin . metabolic syndrome . type-2- diabetes mellitus . lipid prolile

1.0 Introduction

Metabolic syndrome is a collection of medical conditions that can lead to obesity , insulin resistance , cardiovascular disease and hypertension , The prevalence of metabolic syndrome is on a rapid rise due to the shifted paradigm of diet and lifestyle and thus has afflicted many people worldwide (1) , there is still lack of clearly defined pathophysiology and universal definition of metabolic syndrome . Many researchers question is own existence as a specific syndrome that predisposes on individual to particular risk . This has led to several definitions for metabolic syndrome being proposed by various interventional regulatory bodies. World health organization (WHO) defines this syndrome as the presence of glucose intolerance or insulin resistance of diabetics mellitus with any two of the following components: obesity , high serum TG , low HDL-c and hypertension (2). Type-2 diabetes , a scientifically more challenging disease which is characterized by elevated insulin resistance and glucose intolerance . However type 11 diabetes occur as a result of a defect in glucose , lipid and energy homeostasis in organs / systems such as liver , muscle , adipose tissue and gastrointestinal tract . The imbalances in lipid and carbohydrate metabolism cause high levels of serum glucose and free fatty acids which in turn lead to endoplasmic reticular stress in pancreatic beta cells and consequent death (3) . Prolactin is a polypeptide hormone mainly secreted from the auterior pituitary gland and regulated by tonic inhibition of the hypothalamus via dopamine (4,5) . It has been primarily identified as a major stimulatory factor for lactation in the post-partum period prolactin acts through receptors called PRO receptors (PRL_Rs) which are induced as members of the cytokine receptor super family , distributed throughout the immune system monocytes , macrophages , T and B cells , NK cells . Indeed , the relationship between prolactin and immune system has

been demonstrated in the last two decades and has opened new windows in the field of neuro _immuno endocrinology (4). Broadly , in most of previous studies , the correction between prolactin and cardio metabolic risk factors including metabolic syndrome or type -2- diabetes mellitus were not the main focus . Furthermore, previous studies were conducted in comparably small and selected patient population without consideration of major confounding factors (6) . Total cholesterol (TC) represents the total serum cholesterol , it is a necessary molecule in human metabolism , cholesterol is present in the blood in three forms , high density lipoproteins (HDL-c) , low density lipoproteins (LDL-c) and Very low density lipoproteins (VLDL-C) (7,8) . Triacylglycerol (TG) are lipids carried through the blood stream to tissues it is a type of fat the body uses to store energy and give energy to muscles , (7, 9) HDL-c is commonly known as the "good " cholesterol from building up in the arteries , HDL-c is composed of a high proportion of protein with little triacylglycerol and cholesterol , HDL, are involved in reverse cholesterol transport , which is believed to protect against heart diseases and stroke , while LDL-c is sometimes referred to as " bad" cholesterol , this form contains the highest amount of cholesterol , for this reason , LDL-c commonly known as the " bad " cholesterol they contribute to the buildup of plaque within the arteries (7,8). Very low density lipoproteins (VLDL-c) contains very little protein , the main purpose of VLDL-c is to distribute the triacylglycerol produced by liver , A high VLDL-c level can cause the buildup of cholesterol in the arteries and increase risk of heart diseases and stroke (9). Body mass index (BMI) is recommended by WHO as a simple marker to reflect total body fat amount. However, BMI as compared to weight and height is just an index of weight excess rather than body fatness composition (10). Glycated hemoglobin (HbA1c) is formed by posttranslational , non-enzymatic , substrate concentration dependent irreversible process of combination of aldehyde group of glucose and other hexoses with the amino terminal value of the β-chain of hemoglobin (11). Formation of HbA1c is irreversible and the level in Red blood cells depends on the blood glucose concentration (12) , HbA1c is a form of hemoglobin used primarily to identify the average plasma glucose concentration over a prolonged period of time . An increased level of glycated hemoglobin has been associated with cardiovascular disease and diabetes mellitus (6).

2.0 Materials and Methods

2.1 Subjects

In the present study , (70) menopausal women with age in range (45-50) years were enrolled in this study , they have undergone many tests that diagnosed them as diabetic patients with metabolic syndrome , they were newly diagnosed and not given any treatment related to diabetic mellitus or cardiovascular diseases , those patients were compared with a control group consisted of also (70) menopausal women with matched age , they were suffering from diabetes mellitus without any complications such as atherosclerosis and cardiovascular diseases. Blood samples were collected from The National center of Diabetes Treatment and Researches related to Al-Mustansirya university in Baghdad.

2.2 Blood Sampling , parameter determination and calculations

Five milliliters (5 mL) of venous blood were collected from all subjects erolled in this study , placed into plain tubes until coagulation was performed . Serum was separated from blood cells by centrifugation at 4000 r.p.m for 2 min , subsequently serum was divided into small portions and kept frozen (-20 ^{o}C) until analysis , while erythrocytes were used directly to measure HbA1c. Determination of prolactin was performed by Enzyme Linked Immunosorbent Assay (ELISA) for direct antigen detection using high affinity of Biotin for streptavidin which has been coated on the surface of microliter walls , the absorbance was measured at 450 nm. TC and TG were determined by enzymatic methods while HDL-c was determined by precipitation methods , LDL-c and VLDL-c were determined by calculations (13).

LDL-c (mg/dL) = TC – (HDL-c + TG/5)
VLDL-c (mg/dL) = TG/5

HbA_1c was calculated using ion exchange high performance liquid chromatography (HPLC) . Furthermore, women passed through physical examination including weight and height assessment to determine body mass index (BMI) which was calculated in accordance with this equation (14).
BMI = (weight / kg) / (height m^2)

2.3 Statistical Analysis

Results were expressed as mean ±SD (SD : Standard deviation). Student t-test was used to compare the significance of the difference between the studied and control groups . Probability (p-value) ($p<0.001$) , ($p<0.01$) , ($p<0.05$) are statistically considered highly significant , significant and non-significant respectively . The correlation coefficient (r) test is used for describing the positive or negative relationship between prolactin and other studied biochemical parameters.

3.0 Results

Data in table -2- have revealed that prolactin level was significantly decreased ($p<0.01$) in sera of diabetic patients with MS (17.98±8.45) µU / mL compared with diabetic patients without MS (22.87±.78)µU / mL. Moreover , results have suggested that fasting blood sugar was significant increase ($p<0.01$) in sera of diabetic patients with MS (190.94±40.23) mg/dL compared with diabetic patients without MS (119.1±30.12) mg/dL. Furthermore , a non significant increase ($P<0.05$) was shown in HbA1c level in diabetic patients with MS (10.16±1.616)% compared with diabetic patients without MS (7.03±1.14)% . On the other hand , data in table -2- have revealed that TC level was significantly increase ($p<0.01$) in sera of diabetic patients with MS (207.05±39.15) mg/dL in comparison with diabetic patients without MS (196.83±33.59) mg/ dL , also a significant increase ($p<0.01$) was noticed inTG level (0.01) in sera of diabetic mellitus with MS (186.04±45.6) mg / dL compared with diabetic mellitus without MS (120±23.3) mg/dL. Convesely m HDL-c was significantly decrease ($p<0.01$) in sera of diabetic patients in MS (40.48±3.3) mg/dL compared with diabetic patients without MS (46.59±2.5) mg/dL , while a non-significant increase ($p<0.05$) was shown in LDL-c level in sera of diabetic patients with MS (138.56±33.9) mg/dL compared with diabetic patients without MS (129.47±28.33) mg/dL. Also , VLDL-c level was non significantly increase ($p<0.05$) in sera of diabetic patients with MS (28.35±7.98) mg/dL compared with diabetic patients without MS (21.06±6.23) mg/dL. Lastly , BMI was highly significant increase ($p<0.01$) in diabetic patients with MS (31.19±5.79) kg / m^2 compared with diabetic patients with MS (25.93±4.21) kg/m^2. compared with diabetic patients with MS (25.93±4.21) kg/m^2. Results of table -3- indicate results of table-1- and table -2- . It suggests a positive correlation between prolactin and (FBS , TC , TG , LDL-c , VLDL-c , HbA1c) and a negative correlation between prolactin and HDL-c.

Table 1 Prolactin level (µL/mL) , Fasting blood sugar (FBS) (mg/dL) and glycated hemoglobin (HbA1c) (%) in sera of diabetic patients with and without metabolic syndrome (MS).

Parameter	Diabetic Patients Without metabolic syndrome	Diabetic Patients With metabolic syndrome	P value
	Mean ±SD	Mean±SD	
Prolactin (µL/mL)	22.87±4.78	17.98±8.45	P<0.01
Fasting Blood Sugar (mg/dL)	119.1±30.12	190.94±40.23	P<0.01
HbA_{1c} (%)	7.03±1.14	10.16±1.46	P<0.05

Table 2 Total cholesterol (TC) , Triacylglycerol (TG) , high density lipoprotein cholesterol (HDL-c) , low density lipoprotein cholesterol (LDL-c) , Very low density lipoprotein cholesterol (VLDL-c) , and body mass index (BMI).

Parameter	Diabetic Patients Without metabolic syndrome	Diabetic Patients With metabolic syndrome	P value
	Mean ±SD	Mean ±SD	
TC (mg/dL)	196.38±33.59	207.05±39.15	P<0.01
TG (mg/dL)	120.4±23.3	186.04±45.6	P<0.01
HDL-c (mg/dL)	46.59±2.5	40.48±3.3	P<0.01
LDL-c (mg/dL)	129.47±28.33	138.56±33.9	P<0.05
VLDL-c (mg/dL)	21.06±6.23	28.35±7.98	P<0.05
BMI (kg/m^2)	25.93±4.21	31.19±5.79	P<0.01

Table 3 Correlation between prolactin and (TC , TG , HDL-c , LDL-c , VLDL-c , FBS and HbA_{1c}) in sera of diabetic patients with MS.

Parameter	Correlation coefficient (r) with prolactin (µL/mL)	P value
FBS (mg/dL)	+0.530	P<0.001
TC (mg/dL)	+0.390	P<0.05
TG (mg/dL)	+0.445	P<0.001
HDL-c (mg/dL)	-0.690	P<0.001
LDL-c (mg/dL)	+0.313	P<0.05
VLDL-c (mg/dL)	+0.309	P<0.05
HbA_{1c} (%)	+0.143	P<0.05

4.0 Discussion

Prolactin is a pituitary hormone essential for various physiological functions in the human body. It is not only important for the initiation and maintenance of lactation, but also seems to be involved in reproduction growth and development , osmoregulation , immune regulation , brain function , behavior and metabolism (3,6) . The wide expression of prolactin receptors in different tissues and cells such as lymphoid cells , prostate , endometrium , and adipocytes , further suggests the different functions of prolactin (3). Metabolic syndrome represents a cluster of conditions including glucose intolerance, hypertension, dyslipidemia and insulin resistance (1). Prolactin generally is secreted from pituitary gland (4,5). In this regard, a recent study has linked between hypopituitarism (that lead to lower level of prolactin) and metabolic syndrome (15). This discussion give a good support to our results related to prolactin in sera of diabetic patients with metabolic syndrome compared with diabetic patients without metabolic syndrome. As observed from many studies, metabolic syndrome is associated with insulin resistance , elevated glucose and lipids , inflammation , decreased antioxidant activity and hypertension (1,16). These suggestions give a good indication to our results concerned with high fasting blood sugar in sera of diabetic patients with metabolic syndrome compared with diabetic patients without metabolic syndrome. Further, a previous study has shown that the metabolic changes that accompanies hypothyroidism are central obesity, hyperlipidemia, and insulin resistance. These metabolic changes are principally thought to be due to Growth hormone deficiency, although altered insulin – like growth factor -1 , cortisol and gonadotropin metabolism has been implicated. Adult patients with anterior pituitary deficiency and associated growth hormone deficiency have fatty filtration of the liver more frequently than patients with anterior pituitary hormone deficiency without growth hormone deficiency (17) , this study gives a good explanations to our results. Glycated hemoglobin (HbA1c) is widely accepted as a useful measure of mean blood glucose and therapeutic guideline of diabetes. HbA1c is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged period time. Even though insulin resistance is one of the major etiological factors in the development of metabolic syndrome , direct quantitative measurement of insulin sensitivity is not readily available and this cannot be used as the diagnostic tool for the syndrome. therefore , various diagnostic criteria for metabolic syndrome have been suggested. It is shown that patients with high HbA_{1c} significantly define metabolic syndrome (18) , this study has a good agreement with our results related to the higher level of HbA_{1c} in diabetic patients with metabolic syndrome compared with diabetic patients without metabolic syndrome. On the other hand , Dyslipidemia is one of the metabolic risk factors included in metabolic syndrome (19). Hypercholesterolemia is one of the different forms of dyslipidemia , it indicates elevated blood cholesterol. Excess cholesterol builds up in the walls of the arteries, overtime m this buildup contributes to the atherosclerosis , a disease process in which arteries become narrowed and blood flow is impaired (7) , therefore total cholesterol was increased in sera of diabetic patients with metabolic syndrome. Low HDL-c was most frequent while hypertriglyceridemia was least frequent. Abdominal obesity was the second most prevalent factor. This combination of abdominal obesity and low HDL-c was also reported as the most common combination among Chinese type-2- diabetic patients with metabolic syndrome (2). As well ,

Another previous study has suggested that dyslipidemia is a characteristics of the metabolic syndrome which consists of a group of coronary heart disease risk factors that includes higher levels of glucose intolerance (FBS) , TG and lower levels of HDL-c (7) . The simple calculated measure of TG/HDL ratio has been identified as a predictor of insulin resistance and cardiovascular disease and may also be a useful marker of atherogenic lipoprotein profile, enabling them to identify patients who may be at higher risk of metabolic disturbances (26) Three studies cited previously give a good support to our results related to high TG level , low HDL-c level , high BMI and high FBS in diabetic patients with metabolic syndrome. It has suggested that , in diabetic patients with complications (i.e. suffering from metabolic syndrome) , a non-invasive screening for cardiovascular disease is currently recommended . In contrast , in patients without complications , it is very difficult to identify subjects for screening (21). A recent study has revealed that metabolic syndrome accompanied type-2- diabetic patients exhibit a characteristic pattern of abnormalities in serum lipid , dyslipidemia is also characterized by a shift of LDL-c pool toward small , dense LDL-c particles that are cholesteryl ester depleted , this reflect the higher level of LDL-c in sera of diabetic patients with metabolic syndrome compared with metabolic syndrome compared with diabetic patients without metabolic syndrome (22). In this regard , metabolic syndrome include risk factors in adipose tissue dysfunctions and insulin resistance which leads to increase in circulating free fatty acids (FFA) . Increased FFA delivery to the liver increase hepatic secretion and triacylglycerol enrichment of very low density lipoprotein cholesterol (23). This study agree with our results related to the increase in LDL-c and VLDL-c level in sera of diabetic patients with metabolic syndrome compared with diabetic patients without metabolic syndrome. Further , a recent study has suggested that VLDL particles concentration is elevated in metabolic syndrome along with increased large (approximately three fold) and medium (approximately two fold) VLDL particles and that LDL-c concentration is increased as well , along with increased small LDL particles (24). At this point , central abnormalities of dyslipidemia are increased in apoB- carrying lipoproteins and decrease in apolipoprotein A-I lipoproteins . It is believed that this complex dyslipidemia , which is termed atherogenic dyslipidemia , diabetic dyslipidemia or dyslipidemia of insulin resistance , reflects underlying insulin resistance and plays a key role in the increased cardiovascular risk in patients with type-2- diabetic mellitus (22). Interestingly, Hypopituitarism (which lead to low secretion of prolactin) is associated with a complex metabolic impairment and insulin resistance, this recent study highlights the impact of hypopituitarism with regard to BMI and lipid profile by resulting worse than in non hypopituitaric patients , (25) consequently this study indicate the positive correlation between prolactin and (BMI , TC , TG , LDL-c) and the negative correlation between prolactin and HDL-c. Lastly, recent reports have focused on the role of leptin. Leptin levels are significantly increased among patients with hypopituitarism compared with BMI and body fat content-matched control (17). These results strongly indicate the elevation of BMI in diabetic patients with lower prolactin level (with metabolic syndrome) compared with diabetic patients without metabolic syndrome.

5.0 Conclusions

Prolactin could be considered a good biochemical marker for Iraqi menopausal women with metabolic syndrome accompanied by type-2- diabetes mellitus. Moreover, this is the first study in Iraq reported an association between low level of prolactin and type -2- diabetic patients with metabolic syndrome.

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