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CORRELATION BETWEEN CORTISOL AND INSULIN RESISTANCE IN METABOLIC SYNDROME OF IRAQI PATIENTS

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ABSTRACT

Background: Metabolic Syndrome (MS), understood as a complex set of cardiovascular risk factors, related to abdominal fat accumulation and resistance to insulin, is strongly associated with high cardiovascular mortality. Chronic glucocorticoid (GC) exposure in humans is well known to result in whole-body insulin resistance and obesity. **Objective:** The aim of this study is to evaluate the effect of biochemical parameters changes such as cortisol in sera of patients with metabolic syndrome and then assessment their correlations with insulin resistance. **Materials and Methods**: Sample size of the study was 149 persons of both gender selected randomly enrolled in the study which divided into two groups, 80 with metabolic syndrome patients and 69 of apparently healthy individuals as control with their age ranged from (40 to 60) years throughout the period between May. 2019 to Aug., 2020. **Results:**. There was a significant difference between BMI and biochemical parameters (blood glucose, HbA1c, total cholesterol, TG, VLDL-C, LDL-C, Cortisol) in sera of metabolic syndrome patients and healthy control groups ($P \leq 0.01$). The statistical analysis were used in present study was showed a statistical significant between male and female (P value ≤ 0.01). **Conclusion:** There is a significant effect of clinical factors on the incidence and progression of metabolic syndrome disease**.** There is a significant difference in the cortisol levels between male and female MtS patients.

KEYWORDS: MetS, HbA1c, BMI, Cortisol.

INTRODUCTION

Metabolic syndrome (MetS) is a group of risk factors that increase the risk of developing cardiovascular disease and type 2 diabetes mellitus. The risk factors including central obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance **(Paley *et al.* 2018).** The exact cause of metabolic syndrome is unknown. Several features of metabolic syndrome are linked with insulin resistance.

The prevalence of MetS is increasing worldwide but depends in part on the definition used to determine inclusion as well as the composition of the population under study (i.e., gender, age, race, and ethnicity) **[Cornier et al. 2008).**

One of the risk factors included in the syndrome were insulin resistance, defined as the inability of insulin to optimally stimulate the transport of glucose into the body's cell (hyperinsulinemia) **(Reaven GM. 1988).** Most of the metabolic risk factors have no signs or symptoms, although a large waistline is a visible sign. Research on the genetic determinants of metabolic syndrome has broadly taken two approaches, either testing the metabolic syndrome as a whole or as couple of traits, or analyzing correlations with individual components of metabolic syndrome **(Brown *et al.* 2016).**

Insulin resistance is the most frequently associated factor to the singular components of the metabolic syndrome: most authors believe that it may be the common etiological factor. However, visceral obesity seems to be the main driving factor by means of the increased production of free fatty acids whose activity, in turn, might interfere with the action of insulin **(Bosello *et al.* 2000)**.

Insulin resistance is the center underlying the different metabolic abnormalities in the metabolic syndrome, in which pathophysiological conditions insulin becomes less effective in lowering blood glucose. Insulin resistance can be induced by various environmental factors, including dietary habits. Muscle, liver and fat are the three major tissues for maintaining blood glucose levels. In the presence of insulin, fat and muscle cells absorb glucose, and the liver regulates glucose levels by

reducing its secretion and increasing its storage in the form of glycogen **(Fang Hu *et al*. 2013)**.

The higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance **(American Diabetes Association 2009)**.

The elevated levels of glucose and lipids, mainly saturated fatty acids, that are characteristic of insulin resistance synergize at the level of the β-cell to drive parallel increases in reactive oxygen species, and endoplasmic reticulum (ER) stress, all of which culminate in IL-1β secretion and apoptosis Importantly, IL-1β has been a known mediator of β-cell dysfunction and death for more than 25 years **(Kushner *et al.* 2007 and Hotamisligil 2010).**

Increasingly accumulated evidence shows that aberrations in lipid metabolism are the central to the etiology of MS. Triacylglycerol, as an important energy storage form, is closely related to glucose homeostasis and its disregulation is associated with onset of MS such as diabetes, obesity, and cardiovascular diseases **(Fang Hu *et al.* 2013)**.

Glucocorticoids such as cortisol control or influence many metabolic processes, including the formation of glucose from amino acids and fatty acids and the deposition of glycogen in the liver. Glucocorticoids also help to maintain normal blood pressure, and their anti-inflammatory **(Kuo T *et al.* 2015).**

At high concentrations, cortisol antagonizes some of the effects of insulin. It blocks the ability of insulin to enhance uptake of glucose into adipose and muscle cells. It also overrides insulin's ability to suppress the production and release of glucose by the liver. These effects of cortisol can manifest as insulin resistance **(Mendelson 2008)**.

Elevated levels of cortisol, if prolonged, can lead to proteolysis (breakdown of proteins) and muscle wasting **(Simone PS *et al.* 1984).** The reason for proteolysis is to provide the relevant tissue with 'building blocks' for gluconeogenesis **(laycock et al. 2013).**

Indeed, preliminary data suggest that circulating cortisol concentrations are higher in patients with MetS compared with healthy subjects, both in basal conditions and during dynamic stimulation. This difference is more evident in patients with MetS and hypertension or impaired glucose tolerance (IGT) **(Sen, *et al* 2008).** Furthermore, weight loss normalizes cortisol levels and improves insulin resistance **(Reinehr *et al.* 2004).**

The aim of the presented work is to evaluate the effect of some biochemical parameters changes such as cortisol in sera of patients with metabolic syndrome and then assessment their correlations with insulin resistance.

MATERIALS AND METHODS

This work was approved by the Medical Ethics Committee at the College of Medicine/ University of Kerbala. In this cross-sectional study, (149) subjects were recruited, about (80) of them with metabolic syndrome and (69) of apparently healthy individuals. Patients of both gender were randomly selected, with ages ranging from 40 to 60 years. The study was achieved throughout the period from May, 2019 to Aug., 2020.

The samples were collected from Al-Hassan Center for Endocrinology, Al-Hussein teaching hospital, Al-Hussein Medical city, Kerbala health directorate – Iraq. The biomarker parameters and molecular studies were complete research laboratory, Department of Chemistry and Biochemistry, College of the Medicine / University of Kerbala.

According to American Heart Association guidelines (2013), any three of the following traits in the same person meet the criteria for the metabolic syndrome:- obesity (BMI $\geq$ 30 kg/m^2) or abdominal obesity(a waist circumference over 102 cm (40 inches) in men and over 88 cm (35 inches) in women), HDL-C less than 40 mg/dl for men and less than 50 mg/dl for women, fasting blood triglycerides are 150 mg/dL or more, elevated blood pressure of 130/85 mmHg or higher or taking medicine for high blood pressure, fasting blood glucose of $\geq$ 126 mg/dl or above and abnormal cholesterol. Fasting blood glucose, insulin, HbA1c, lipid profile and cortisol and BMI have been determined in all control and patients included samples in the study.

Statistical analysis was used by SPSS software version 20, and a p-value less than 0.05 was considered statistically significant in all variable, continuous and discrete variables using numbers and percentages.

RESULTS

The results of present study were revealed in figure (1) the distribution of sample according to the gender, the number of males had metabolic syndrome were (55) and female (34), while in healthy control the number of males were (26) and female (35).

The statistical analysis were used in present study was showed a statistical significant between male and female (P value $\leq$ 0.01).

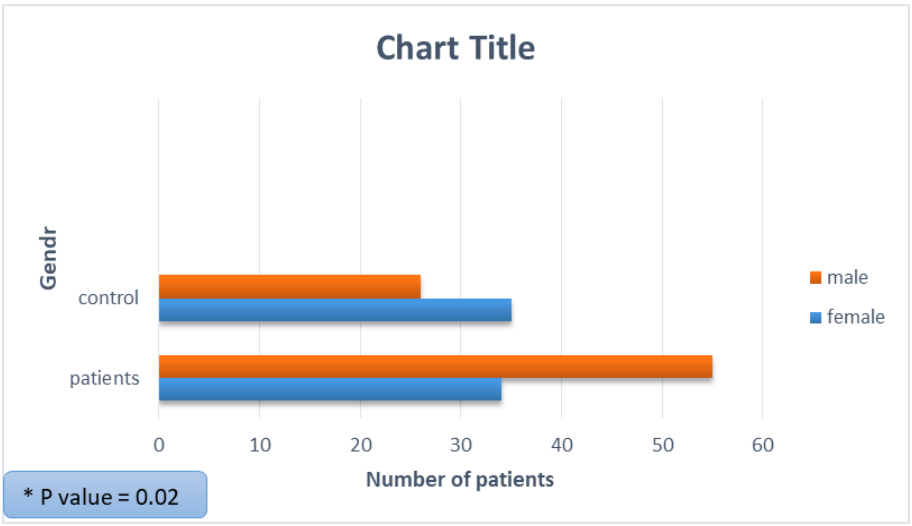

Fig. 1: Gender relationship between metabolic syndrome patients and healthy control.

The age groups that appeared in figure (2) divided into three groups:

a. 40 - 49 years the number of metabolic syndrome patients is (39 and in healthy control is (28).
b. 50 - 59 years0t he number of metabolic syndrome patients is (37) and in healthy control is (36).
c. The third group ≥ 60 the number of metabolic syndrome patients is (4) and in healthy control is (5).

In this study most of metabolic syndrome patients were found in age group (40 - 49) years, the lowest number were in the age group (≥ 60) years, there is non-significant result (P value = 0.6) were revealed in present study and the statistical test has been used in the current study namely Chi square test.

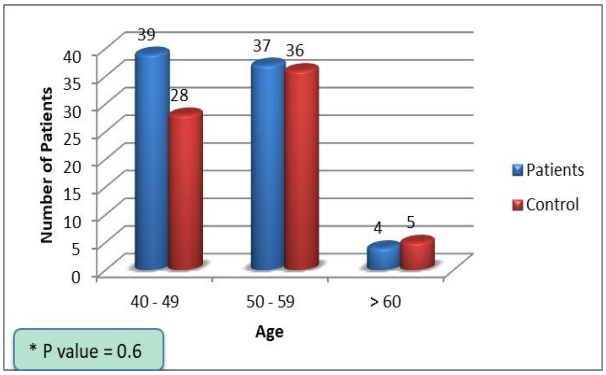

Fig. 2: Number of metabolic syndrome patients and healthy control based on age groups.

Table 1: Association between biochemical parameters with metabolic syndrome and healthy control.

Parameters	Mean ± SD		*P value*
	Patients	Control	
Blood glucose, mg/dl	244.3 ± 98.3	111.3 ± 22.1	*≤ 0.01*
HbA1c%	9.3 ± 2.15	5.9 ± 0.6	*≤ 0.01*
Insulin, µIU/mL	14.8 ± 4.5	13.8 ± 2.7	*0.098*
TC, mg/dl	178.3 ± 47.32	121.01 ± 22.9	*≤ 0.01*
TG, mg/dl	254.3 ± 101.5	111.8 ± 23.1	*≤ 0.01*
HDL-C, mg/dl	34.95 ± 9.96	34.1 ± 6.5	*0.57*
VLDL-C, mg/dl	50.8 ± 20.8	21.8 ± 4.5	*≤ 0.01*
LDL-C, mg/dl	100.7 ± 43.3	62.1 ± 26.03	*≤ 0.01*
BMI	37.5 ± 1.9	32.5 ± 3.1	*≤ 0.01*
Cortisol	20.8 ± 4.2	13.9 ± 1.9	*≤ 0.01*

HbA1c: glycated hemoglobin A1c. TC: total cholesterol. TG: triglyceride. HDL-C: High density lipoprotein- cholesterol. LDL-C: Low-density lipoprotein- cholesterol. VLDL-C: very Low-density lipoprotein- cholesterol. BMI: body mass index.

The data obtained in this study was shown in table (1). There was a significant difference between biochemical parameters (blood glucose, HbA1c, total cholesterol, TG, VLDL-C, LDL-C, Cortisol and BMI) in metabolic syndrome patients as compared with healthy control groups ($P \leq 0.01$).

While a non – significant differences between metabolic syndrome patients and healthy control groups of insulin ($P = 0.098$) and HDL-C (P = 0.57) were observed.

DISCUSSION

A significant relationship was found between metabolic syndrome and gender, as the prevalence of the disease in men was more than in women when comparing patients

with healthy subjects, the (P value ≤ 0.01), but this does not exclude the presence of a large proportion of women who had The factors risk of MetS disease.

The most prevalent combination of MetS components for both genders was the clustering of TG, BP, and BS. However, the clustering of high TG levels, high BP, and elevated BS levels was more prevalent for males (30.8 %) than females (14.5 %; p <0.001) **(Sangjin Lee *et al.* 2016).**

Metabolic syndrome showed an association with advanced age for both men and women (P < 0.001 for both), with greater prevalence of MetS in young and middle-aged men than in women (6.7%–39.9% vs 3.3%–36.4%); these patterns were reversed in people 60 years or older (34.0%–40.5% vs 55.2%–64.1%) **(Park E *et al.* 2015).**

Figure (2) was showed that the higher incidence of MtS is in (40-49) age group. In many countries, the prevalence of the metabolic syndrome appears to be increasing along with BMI, especially in younger individuals. Onset varies from adolescence in the most severe cases to the very elderly. Prevalence varies markedly by race/ethnicity and the environment **(M. Alexander et al. 2003).**

Significant results were observed between biochemical markers investigated and metabolic syndrome. The results obtained show that serum FBS was significantly high in T2DM patients group compared with normal control group (P < 0.001). FBS sounds more reliable to separate diabetics from non-diabetics. However, in any case one would like to use HbA1c in screening, the conventional cutoff points of 6% is an acceptable threshold for discrimination of diabetics and non-diabetics, although 6.15% increased slightly the overall accuracy **(Ghazanfari *et al.* 2010).**

The results obtained showed that serum TG, total cholesterol, LDL-C show significant elevate P>0.001 in T2DM patients group compared with normal control group, while serum HDL-C level show non-significant decrease P<0.05 compared with normal control group as show in table (3). The present study showed a relationship between diabetes and increase appetite, which leads to increase bad cholesterol and decrease HDL-C this finding consist with previous reported about correlation between diabetes and decrease HDL-C levels **(Neeli *et al.* 2009)**.

The higher prevalence of high TG relative to most of the studies elsewhere might be due to higher intake simple carbohydrates and higher ratio of simple to complex carbohydrate consumption by the Persian people **(Bahreinian and Esmaillzadeh 2012).** It was observed that higher prevalence of hypertriglyceridemia in Iranian males similar to findings in most other countries **(Tabatabaei-Malazy *et al.* 2014).**

The prevalence of dyslipidemia varies widely according to the ethnic, socioeconomic, and cultural characteristics of distinct population groups **(Bayram *et al.* 2014),** hypertriglyceridemia was independently associated with diabetes mellitus. A similar association between hypertriglyceridemia and HbA1c was reported in a Russian study **(Karpov and Khomitskaya 2015).**

The present study showed the independent risk factors of the different types of dyslipidemia by multivariate analysis. Diabetes mellitus and hypertension were independent risk factors for hypercholesterolemia. A study from Saudi Arabia also reported same association between diabetes mellitus, hypertension, and hyper-cholesterolemia **(Abujbara, *et al*. 2018).**

In 1988, Reaven hypothesized that insulin resistance is a common link in causing hyperglycemia and other cardiovascular risk factors (syndrome X). Although other additional factors (such as obesity) appear to be involved in the pathogenesis of the disease, the common link suggested by Reaven served as a catalyst for bringing together researchers in cardiovascular disease and diabetes. The link between these disciplines was strengthened because most type 2 diabetes patients die as a direct result of cardiovascular disease and because hyperglycemia is common in patients with heart disease **(Alexander *et al.* 2006).**

Statistically significant differences were found between the different BMI-MetS classes with respect to all variables included in the MetS.

The most common component of metabolic syndrome in the sample was shown to be central obesity and diabetes mellitus followed by hyper-triglyceridemia and hypertension; this disagrees with the Indian study, which showed that the main component was hypertension (98.37%), followed by dyslipidemia (77.05%), hyperglycemia (75.41%), and obesity (59.02%) **(Jaspinder Kaur *et al.* 2014).**

Most of the obese individuals who showed metabolic syndrome were not exercising, but no significant association was found between metabolic syndrome and practicing exercises. The heritage family study in the United States showed that exercise training resulted in improvement in the metabolic profile of the participants; the prevalence of metabolic syndrome was decreased from 16.9% before training to 11.8% after training **(Katzmarzyk *et al.* 2003).**

The prevalence of most features of MetS and other risk factors for diabetes or cardiovascular disease increased with increasing BMI in people with or without MetS, although the trend to increase risk factors was more pronounced across BMI categories among people without MetS. 32% of people with MetS and normal weight were insulin resistant, 34% of obese people without MetS were insulin resistant, and 68% of obese

people using MetS were insulin resistant **(Meigs, J. B. *et al.* 2006).**

The cortisol has significant impact on metabolic syndrome patients and this agree with anagnostis and his group research. Emerging data suggest that patients with MetS show hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to a state of "functional hypercortisolism."The cause for this activation of the HPA axis remains uncertain but may be partly associated with chronic stress and/or low birth weight, which are both associated with increased circulating cortisol levels and greater responsiveness of the HPA axis. Increased exposure to cortisol contributes to increased fat accumulation in visceral depots. However, cortisol metabolism is not only centrally regulated. The action of 11β-hydroxysteroid dehydrogenase-1 at the tissue level also modulates cortisol metabolism. Increased 11β-hydroxysteroid dehydrogenase-1 activity in adipose tissue and liver might contribute to the development of several features of the MetS **(Anagnostis Panagiotis et al. 2009)**.

In a study by Roy et al., 1990 regarding hypothalamic-pituitary-adrenal axis disorder in diabetic patients, glucocorticoid and cortisol secretion were higher in patients with type 2 diabetes mellitus and insulin resistance. Regarding this study, an increase in cortisol secretion leads to diabetes and makes metabolic control difficult. In the current study, similar to Roy study, cortisol secretion has been observed to be higher in people with diabetes than healthy subjects, but no results on the effects of cortisol secretion on diabetes occurrence have been achieved **(Roy M. *et al.* 1990)**

The effects of cortisol on lipid metabolism are more complicated since lipogenesis is observed in patients with chronic, raised circulating glucocorticoid (i.e. cortisol) levels **(laycock *et al.* 2013**), although an acute increase in circulating cortisol promotes lipolysis. The usual explanation to account for this apparent discrepancy is that the raised blood glucose concentration (through the action of cortisol) will stimulate insulin release. Insulin stimulates lipogenesis, so this is an indirect consequence of the raised cortisol concentration in the blood but it will only occur over a longer time scale (**Djurhuus *et al.* 2002)**.

CONCLUSION

The effect of the risk factors (blood glucose, HbA1c, TC, TG, VLDL-C, LDL-C and BMI) on metabolic syndrome disease was observed significantly thus these risk factors are threatening for heart diseases in MetS patients as compared with control group.

There is significant association between cortisol and insulin resistance because of the effect of cortisol that increase the glucose in the body.

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