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Component of Metabolic Syndrome with High Sensitive C-Reactive Protein, TSH and Associations between them in Sujects of Hilla City (Iraq)

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ABSTRACT

Metabolic syndrome (MS) is a group of risk factors that predispose to cardiovascular diseases (CVD). C-reactive protein (CRP) levels correspond with individual components of the metabolic syndrome ,and a relation exists between elevated CRP levels and cardiovascular risk factors. Elevation in CRP levels could be related to inflammatory thyroid disease .Low TSH(Thyroid-Stimulating Hormone) levels also have effects on the cardiovascular system. This study aimed to study the levels of serum CRP, TSH and associations with metabolic syndrome in both gender.Forty subjects with MS comprised the study group and 30 subjects without MS were in the control group, with age range 35–65 years. About 5ml of fasting blood (8-12 h.) was collected from each individual. To determine serum C-reactive protein (CRP), TSH(Thyroid-Stimulating Hormone), T3(Triiodothyronine) and T4 (Thyroxin) the quantitative sandwich enzyme immunoassay technique were used. Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c) and Lipid profile were measured by an enzymatic colorimetric(GPO-POD) method. The present study show significant differences between metabolic patients and control group. There were significant elevation ($P<0.05$) in Waist circumference (WC), Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), C-reactive protein (CRP),Triiodothyronine(T3), Thyroxin(T4) and Triglyceride(TG) ,while Thyroid stimulating hormone(TSH) show significant decrease ($P<0.05$) in metabolic patients than control group, whereas the results of BMI(Body mass index), Systolic(SBP) and diastolic(DBP) blood pressure ,Cholesterol, HDL(High density lipoprotein), LDL (Low density lipoprotein) and VLDL (Very low density lipoprotein) show no significant differences ($P > 0.05$) between metabolic groups and control. According to gender the results show significant elevation ($P<0.05$) in WC in females than males and significant elevation ($P<0.05$) in TG in males than females, while other parameters show no significant differences ($p>0.05$) between males and females.Correlation analysis showed no significant correlation between CRP with other parameter in both metabolic patients and control group. Our results showed strong association among pro-inflammatory state , decrease serum TSH levels with MS which representing an emerging risk factors for cardiovascular risk.

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INTRODUCTION

Metabolic syndrome (MS) is a group of risk factors that predispose to cardiovascular diseases (CVD). They include: central obesity, raised triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), raised blood pressure (BP) and raised fasting blood glucose. Presence of three or more of these risk factors indicates MS. It is also associated with a pro-thrombotic and a pro-inflammatory state, which have been implicated in development of MS. These include: non-esterified fatty acids (NEFAs), inflammatory cytokines, plasminogen activator inhibitor-1 and resistin (Hanley *et al*.,2005; Bener *et al*.,2010; Muraleedharan and jones,2010 ; McCullough,2011;Marjani and Shirafkan,2011).

Several new features have been added to the syndrome over time. These include elevated plasminogen activator inhibitor-1 (PAI-1) concentrations and now, elevated C-reactive protein (CRP) concentrations. These features were added on the basis that they were frequently found in association with the metabolic syndrome. These features are probably related to both insulin resistance and obesity (Dandona *et al*.,2005).

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Taking into consideration gender specification, this disease is rifer in females than males. Females show greater incidence of abnormalities in most of the criteria used in the diagnosis of metabolic syndrome, especially obesity, hypertension and dyslipidemia. Adiposity is correlated with altered production of adipocytokines and inflammatory mediators which are the source of angiopathy and vascular damage (Ahmed *et al*.,2011).

Type 2 diabetes(T2DM) could be considered as an inflammatory disease that is largely based on reports stating that increased levels of inflammatory markers , including CRP (Hasan *et al*.,2012).

The changes in lipid metabolism seen with abdominal fat accumulation have been well characterized and include hypertriglyceridemia, reduced HDL cholesterol, and increased numbers of small, dense LDL particles (Carr and Brunzell,2004;Sancho-Rodriguez *et al*.,2011).

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization. The resulting hyperinsulinemia and hyperglycemia, as the release of adipocyte cytokines, have been shown to induce vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which are atherogenic .Inflammation has been implicated in MS pathogenesis, especially as a mechanism of insulin resistance and endothelial dysfunction . This enlarged mass of adipocytes plays a vital role in the pathophysiology of MS. There is increased flux of free fatty acids into the liver leading to excessive hepatic production of triglycerides and resultant hypertriglyceridemia. Moreover, the adipocytes also secrete inflammatory cytokines (e.g., Monocyte chemoattractant protein–1 (MCP-1), Tumor Necrosis Factor Alpha (TNF-α), Interleukin -6(IL-6), leptin and C- reactive protein), while there is relative deficiency of the anti-inflammatory and antiatherogenic cytokine adiponectin, resulting in a low-grade inflammatory state thought to be responsible for insulin resistance and endothelial dysfunction (Regitz-Zagrosek *et al*.,2006;Ahmed *et al*., 2010;Raimundo and Lopes, 2011).

Athyros *et al*.,(2011) revealed that visceral adiposity, a marker of "dysfunctional adipose tissue", plays a key role in the development of the MS and T2DM. It is characterized by accumulation of fat in the central part of the body and correlates with insulin resistance (IR). Visceral adipocytes are large, insulin-resistant and highly active metabolically. Through the production of a variety of adipokines, adipocytes play a role in the pathogenesis of inflammation, dyslipidaemia and hypertension.

C-reactive protein (CRP) is a sensitive marker for systemic inflammation and is produced by the liver . A relation exists between elevated CRP levels and cardiovascular risk factors, fibrinogen, and high density lipoprotein(HDL) cholesterol, suggesting that inflammation occurs throughout life in the development of atherosclerosis and cardiovascular disease. Elevated CRP concentrations can be related to the increased expression and release of interleukin-6 (IL-6) by adipose tissue. IL-6, a pro-inflammatory cytokine, stimulates the production of CRP in the liver. In obese subjects, a strong correlation exists between obesity and IL-6 levels. IL-6 is essential for the induced expression of CRP, suggesting that elevated CRP levels are secondary to increase in IL-6 secretion. A linear increase in CRP levels with an increase in the number of metabolic disorders was noted(Das *et al*.,2002; Ridker *et al*.,2003;Ravaglia *et al*.,2006).

Low-grade systemic inflammation, mainly characterized by increased levels of circulating C-reactive protein (CRP), is associated with an increased risk of cardiovascular disease (CVD). Obese individuals have significantly higher CRP levels than non obese subjects. One possible link between CRP and obesity assessed by body mass index (BMI) could be the cytokine production by adipose tissue. Among these cytokines, IL-6 is known as the major regulator of acute phase protein synthesis as clearly demonstrated in human hepatocytes (Maachi *et al*., 2004).

Saleem *et al*., (2011) show that the Thyroid-stimulating hormone (TSH) correlates directly with insulin resistance, TG and indirectly with HDL-C in subjects within normal thyroid function. TSH levels were found to be significantly associated with MS.

Also Ross *et al*., (2007) found that concentrations of free T3 (FT3) are associated with insulin production and hyperinsulinemia .In the same study population, it was found that insulin resistance modifies the relationship between levels of TSH and low density lipoprotein cholesterol (LDL-C) .

MATERIAL AND METHODS

This was an analytical, cross-sectional study that carries out in 2013. It was conducted at diabetic center in Mergan hospital, Babylon province. Forty subjects with MS comprised the study group and 30 subjects without MS were in the control group, with age range 35–65 years. Three or more of the following five criteria indicated MS according to the National Cholesterol Education Program- Adult Treatment Panel III (NCEP ATP III) definition:

1. Raised BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg) or drug treatment for raised BP.
2. Central obesity (waist circumference ≥102 cm in men and ≥88 cm in women).
3. Raised fasting blood glucose (≥100 mg/dl) or drug treatment for raised blood glucose.
4. Raised serum TG (≥150 mg/dl).
5. Low serum HDL-C (<40 mg/dl in men and <50 mg/dl in women).

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Subjects with thyroid disease, those with history of thyroid drug use, history of steroid use and those who have had thyroid surgery were excluded from the study. Systolic and diastolic BP was measured after 5 minute rest using sphygmomanometer. Hypertension was defined as systolic ≥140 mm Hg, diastolic blood pressure ≥ 90 mm Hg. Five ml of venous blood was drawn in the morning after an overnight fast of 8–12 hours. Serum was separated after centrifugation for hormonal analysis and stored at a temperature of -80 °C until analysis. The serum TC, TG and HDL-C were analyzed by enzymatic method (CHOD-PAP). The LDL-C was calculated by the following equation: LDL-C = TC – HDL-C – (TG × 0.2). Serum fasting glucose and glycosylated hemoglobin (HbA1c)were analyzed using the colorimetric-enzymatic method with glucose oxidation .Body mass index (BMI) was calculated using the formula BMI= weight (kg)/ height^2 (m)^2 and classifying under weight (BMI<18), normal (BMI 18 - 24.9), overweight (BMI 25 - 29.9) , obesity (BMI 30-39.9) and morbid obesity (BMI > 40) (WHO,2004).The waist circumference was measured while the subject standing up , at the narrowest point of the torso width-wise, usually just above the belly button ,which is ≤102 cm in male and ≤ 88 cm in female (WHO,2004).

The analyses were performed using the statistical package for social sciences (SPSS version 17.0). Physiological and biochemical parameters data were analyzed using factorial experiment with completely randomized. Data were represented as mean ± SD. Bivaraite correlations were performed using the Pearson correlation coefficient .P value (P<0.05) was considered statistically significant.

RESULT:

The present study show significant differences between metabolic patients and control group(Table 1).There were significant elevation (P<0.05) in Waist circumference(WC) , Fasting blood glucose (FBG) , glycosylated hemoglobin (HbA1c), C-reactive protein (CRP),Triiodothyronine(T3), Thyroxin(T4) and Triglyceride(TG) ,while Thyroid stimulating hormone(TSH) show significant decrease (P<0.05) in metabolic patients than control group, whereas the results of BMI ,Systolic(SBP) and diastolic(DBP) blood pressure ,Cholesterol , HDL , LDL and VLDL show no significant differences (P > 0.05) between metabolic groups and control. According to gender the results show significant elevation (P<0.05) in WC in females than males and significant elevation (P<0.05) in TG in males than females, while other parameters show no significant differences (p>0.05) between males and females.

Correlation analysis showed no significant correlation between CRP with other parameter in both metabolic patients and control group (Table 2).

DISCUSSION:

In our study metabolic syndrome was found to be more common in female as compared to their male counterparts(Table 1). This high incidence of obesity contributes to a very high frequency of metabolic syndrome in our patients, especially women. Physical inactivity and excess weight have been shown to be the main underlying contributors to the development of metabolic syndrome(Ahmed *et al*.,2010).Central obesity plays a central role in the development of the MS and appears to precede the appearance of the other MS components(Ogbera,2010).

The mechanism by which excessive body fat causes insulin resistance and impairs glucose metabolism is not clearly defined, but fat stores are an important cause of increased free fatty acid and triglyceride in the skeletal muscle, which impairs insulin secretion(Juda *et al*., 2010; Bener *et al*., 2010; Ahmed *et al*., 2010; Marjani and Shirafkan , 2011).

The present study show significant elevation in WC in metabolic patients (Table 1),this may be because an increased waist circumference is most likely associated with elevated risk factors because of its relation with visceral fat accumulation and the mechanism may involve excess exposure of the liver to fatty acids . The abdominal visceral adipose tissue deposition is associated with an increase of the portal free fatty acid concentration, which leads to plasma disturbances as hyperinsulinemia(Ahmed *et al*.,2011;Shirafkan and Marjani,2011).

Clinical evidence suggests that the association of diabetes with central obesity is stronger than the association with general fat. Waist circumference has been used as measures of central obesity and body mass index has been used as a measure of general obesity. Central obesity has been associated with decreased glucose tolerance, alterations in glucose insulin homeostasis, reduced metabolic clearance of insulin, and decreased insulin-stimulated glucose disposal (Kamath *et al*.,2011; Shirafkan and Marjani,2011).

We found differences by gender in waist circumference between metabolic patients and control group (Table 1), which is supported by study of Sancho-Rodriguez *et al*.,(2011) who found that there was sex differences in waist circumference between patients with and without MS.

There was significant elevation in FBG and HbA1c in metabolic patients than control group while there was no significant differences between males and females in both groups (Table 1).Individuals with impaired fasting glucose and prone to develop overt diabetes tends to gain visceral fat more selectively than subcutaneous fat, compared with those who remained non diabetic. This could be sustained by defects in adipogenesis or

specificities in adipose tissue morphology, independently of body fat level (Kamath *et al*.,2011).The levels of HbA1c and FBG did not differ significantly between male and female, similar observation were also obtained by VinodMahato *et al*., (2011).

Persistent hyperglycaemia causes glycosylation of all proteins, as a result elevation in HbA1c and collagen cross linking and matrix proteins of arterial wall. This eventually causes endothelial cell dysfunction, contributing further to atherosclerosis (Uttra *et al*., 2011)

Visceral obesity is also associated with increased free fatty acid release into the portal vein .This leads to increased hepatic glucose output with resultant hyperglycemia and decreased hepatic insulin extraction with resultant hyperinsulinemia(Lane,2004).

There were no significant differences in blood pressure between metabolic patients and control group in both gender (Table 1), this may be due to hypertension is not strongly linked to the metabolic syndrome (Ford *et al*.,2002).

In the present study metabolic syndrome was associated with high CRP (Table1). CRP levels correspond with individual components of the metabolic syndrome (Ridker *et al*., 2003; Ravaglia *et al*.,2006).

Measurement of CRP is the most practical way to assess the presence of an inflammatory state. CRP levels tend to be higher than normal in patients with the metabolic syndrome. An elevated CRP (≥3 mg/L) is an emerging risk factor for cardiovascular disease (CVD)(Grundy *et al*.,2004).

Increased circulating inflammation markers could be predictive of CVD. Among the inflammation markers available, hs-CRP appeared as one of the most powerful independent predictors of cardiovascular events. CRP has been linked to the degree of obesity and it has been proposed that cytokines such as IL-6 and TNFα could be a link between BMI, CRP and CVD. These cytokines could be secreted by adipocytes and by inflammatory cells such as macrophages present in adipose tissue from obese subjects. CRP could be deleterious on the arterial wall since it has been found to promote directly endothelial cell inflammation and atherosclerotic processes. Therefore, to reduce CRP levels could help to prevent vascular damage (Maachi *et al*.,2004).

There is growing evidence that subclinical inflammation might be responsible for dysfunctions in lipid metabolism and moreover for the increasing risk of cardiovascular complications. Overall it can be noted that CRP levels are higher in women than in men and that they are positively correlated with the BMI (Starcke and Vollmer,2006).In diabetic subjects testosterone is inversely proportional to CRP and IL-6(Jones,2007).

Testosterone has been shown to suppress the expression of IL-6, IL-1b and TNFα in human cell lines and stimulating production of anti-inflammatory IL-10. In men with type 2 diabetes highly sensitive C-reactive protein (CRP) and IL6 also are inversely correlated with testosterone (Muraleedharan and jones,2010). Females have higher CRP values than males (Wang and Hoy,2005). Estradiol(E2) may actually encourage macrophage CRP production under conditions of high sdLDL-C, ,theCRP gene response to E2 was significantly correlated with plasma sdLDL-C levels, with a greater increase in CRP expression in subjects with higher sdLDL-C levels(Corcoran *et al*.,2010).

Elevation in CRP levels could be related to inflammatory thyroid disease (Luboshitzky & Herer,2004).Thyroid hormones influence carbohydrate metabolism in skeletal muscle and adipose tissue via the positive transcriptional regulation of the muscle/fat-specific glucose transport 4 (GLUT4), and stimulate lipolysis. All these steps interact with insulin action (Park *et al*.,2011).

There was significant decrease in TSH and significant elevation in T3and T4 in metabolic patients than control group (Table 1),this may be belong that more individuals with decreased serum TSH levels died quicker than individuals with serum TSH levels within the reference range (Biondi,2010). Low TSH levels also have effects on the cardiovascular system (Hergen *et al*.,2005).

Hyperthyroidism has profound effects on cardiovascular system, including reduced systemic vascular resistance due to relaxation of vascular smooth muscle cells, enhanced heart rate and cardiac output due to increase in cardiac diastolic relaxation, contractility and heart rate (Sütken *et al*.,2009).

Subjects with decreased serum TSH levels had increased odds for the presence of carotid plaques compared with those with normal serum TSH levels. The occurrence of carotid plaques is associated with generalized atherosclerosis, that have demonstrated higher values of the intima-media thickness (IMT) of the common carotid artery in subjects with decreased serum TSH levels compared with euthyroid subjects. Increased IMT of the common carotid artery has been shown to be a valid marker of both coronary, and generalized atherosclerosis, as well as a predictor of future cardiovascular events. Our observation is further strengthened by the data on stroke prevalence that was also higher in subjects with decreased serum TSH compared with those with normal levels (Dorr *et al*.,2008).

Serum TG and TG/HDL-C ratio, which are surrogate markers for insulin resistance, were significantly elevated in study group compared to control group (Table1). This indicates that the study group may have greater insulin resistance than the control group. Insulin resistance is said to be a common underlying abnormality in MS (Saleem *et al*.,2011).

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Increased triglyceride levels together with decreased HDL-cholesterol levels appear to be the most serious combination for accelerating vascular damage. This combination represents a continuous higher stress on the endothelium and the whole vascular wall due to flawed transport (Kubesova *et al*.,2011).

Dyslipidaemia in diabetes is characterized by elevated plasma triglycerides and very low-density lipoproteins (VLDL), reduced high-density lipoprotein cholesterol (HDLC) and a shift in low- density lipoprotein (LDL)distribution towards small, dense particles (Igwe *et al*.,2008; Otamere *et al*.,2011;VinodMahato *et al*.,2011).

No significant correlation was observed between hs-CRP and FT3, FT4, and TSH in study group(Table 2), this result is in agreement with the study of Güldiken *et al*., (2005) who found no significant correlation between hs-CRP and FT3, FT4, and TSH in hyperthyroid group.

In conclusion, the results of the present study show that there was strong relationship between high CRP and low TSH with MS which may predict to the cardiovascular risk factors.

Table 1: Comparison between metabolic syndrome and control subjects for both gender.

Parameter	Control N=30		Metabolic syndrome(MS) N=40		P value of group	P value of gender
	Male(N=15) Mean± SD	Female(N=15) Mean± SD	Male(N=18) Mean± SD	Female(N=22) Mean± SD		
BMI(kg/m²)	29.36±6.48	31.12±5.90	30.99±3.33	30.03±3.37	0.53	0.71
WC(cm)	90.75±10.64	101.75±11.23	101.6±6.22	103.19±8.86	0.02*	0.001*
SBP mm Hg	122.17±11.1	127.17±12.3	132.2±11.9	131.2±12.1	0.06	0.08
DBP mm Hg	80.05±7.8	78.06±9.3	82.17±8.8	83.01±9.2	0.77	0.55
FBG(mmol/l)	5.01±0.56	5.52±0.77	13.27±2.95	11.09±3.90	0.001*	0.67
HbA1c(%)	5.22±1.03	4.62±0.75	7.37±1.01	8.42±1.71	0.001*	0.77
CRP(mg/l)	1.3 ± 0.1	1.56 ± 0.05	2.54 ± 0.53	2.59 ± 0.53	0.001*	0.49
TSH(mIU /ml)	2.56 ± 0.65	2.52 ± 0.94	1.94 ± 0.94	1.76 ± 0.92	0.01*	0.73
T3(ng/ml)	0.50 ± 0.07	0.60 ± 0.08	0.78 ± 0.12	1.01 ± 0.08	0.02*	0.29
T4(mg/dl)	5.17 ±0.37	5.57 ±1.57	10.89 ± 2.43	10.01 ± 3.64	0.01*	0.75
Cholesterol (mmol/l)	4.11±1.00	4.01±0.58	4.44±1.23	4.27±1.05	0.14	0.55
TG(mmol/l)	1.62±0.81	1.11±0.16	2.02±0.60	1.71±0.04	0.02*	0.03*
HDL(mmol/l)	1.00±0.21	1.13±0.11	1.03±0.13	1.12±0.20	0.58	0.07
LDL(mmol/l)	2.51±0.88	2.59±0.78	2.96±0.12	2.85±0.28	0.25	0.55
VLDL(mmol/l)	0.56±0.04	0.48±0.01	0.62±0.03	0.60±0.01	0.15	0.50

BMI: Body Mass Index, WC: Waist Circumference, BP: Blood Pressure, FBG: Fasting Blood Glucose, HbA1c : Hemoglobin A1C (glycosylated hemoglobin), C-reactive protein (CRP), Thyroid stimulating hormone(TSH),Triiodothyronine(T3), Thyroxin(T4), TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein. *P value is significant ≤ 0 .05 level, SD :Standard deviation.

Table 2: The correlation among CRP with anthropometrical measurements and TSH in control and metabolic patients for both gender.

Groups	Index		BMI	WC	TSH	T3	T4
Control	CRP in male (N=15)	r	0.01	0.81	0.98	-0.90	0.50
		p	0.98	0.39	0.10	0.27	0.66
	CRP in female (N=15)	r	-0.83	-0.97	0.99	-0.94	0.90
		p	0.37	0.13	0.06	0.21	0.28
MS	CRP in male (N=18)	r	-0.10	0.22	-0.06	0.29	-0.43
		p	0.71	0.40	0.80	0.26	0.09
	CRP in female (N=22)	r	-0.29	0.04	0.06	0.31	0.33
		p	0.29	0.86	0.83	0.25	0.21

Correlation coefficient (r) ,* Correlation is significant ≤ 0.05 level (2-tailed).

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