

Assessment of High Sensitivity C.Reactive Protein in male patients with metabolic syndrome and atherosclerosis complications

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Abstract

Background: syndrome X or metabolic syndrome is a collection of multiple diseases mainly visceral obesity , hypertriglyceridemia , decrease HDL level, hypertension and elevated fasting blood glucose that lead to accelerated atherosclerosis through multiple mechanisms, one of the most important is increase inflammation of the vessels manifested by elevated high sensitivity C reactive protein (hs-CRP).

Objective: The aim of the study was to assess the prevalence of elevatedhs CRP in people with metabolic syndrome and atherosclerosis complication (IHD, Cerebrovascular disease, peripheral vascular disease) and metabolic syndrome without these complication.

Patients and methods: This is a cross sectional study carried out in Diabetic referral center in Baghdad al-rusafa extended from November 2009 to March 2010 for 84 male patients with metabolic syndrome ,aged 40-70 years, clinical features ,anthropometric and biochemical measurement (BP, Waiste circumference, BMI, HDL, LDL, TG, BG, hs CRP) were recorded and metabolic syndrome diagnosis was made according to IDF definition

Results: The 84 patients with metabolic syndrome divided in to two groups the first 35 patients

clinically complicated atherosclerotic group were 30 patients high risk 85% and 5 patients low risk 15%. The second 49 patients (clinically uncomplicated atherosclerotic) group were 30 patients high risk 61% and low risk 19 patients 39%, and tabulated with the p.value was (0.014).

These results tabulated with the following parameters ,waist circumference (abnormally high p.value was 0.05, normal p.value was 0.49) ,blood pressure (hypertension p.value was 0.05 and normal blood pressure p.value was 0.58),age(middle age p.value was 0.007 and elderly age p.value was 0.29) and BMI(less than 25g/kg p.value was 0.39 and more than or equal to 25 g/kg p.value was 0.08).

Conclusion: The values of hs-CRP are high in most patients with metabolic syndrome but are higher in patients with atherosclerotic complications than those without .specially elevated in those with hypertension ,middle age group, increasing waist/hip ratio with significant p.value,and in high BMI but with insignificant p.value.

Key words : (HS-CRP metabolic)

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Introduction

The metabolic syndrome consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM)(1).The underlying causes of the syndrome are genetic and environmental: overweight, obesity, and physical inactivity, which lead to insulin resistance, hyperinsulinemia, endothelial dysfunction, and inflammation(2). Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in an increased production of glucose, triglycerides and secretion of very low density lipoproteins (VLDLs). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased density of low-density lipoproteins (LDLs). FFAs also

reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). Increases in circulating glucose, and to some extent FFA, increase pancreatic insulin secretion, resulting in hyperinsulinemia.Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to the hypertension, as might increase levels of circulating FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs.The enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor(TNF) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating

FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, and insulin resistance in muscle. Cytokines and FFAs also increase the hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic state. Higher levels of circulating cytokines also stimulate the hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin sensitizing cytokine adiponectin are also associated with the metabolic syndrome(1). There are multiple clinical presentations; diabetes, hypertension(3), dyslipidemia(4), nonalcoholic fatty liver disease (NAFLD)(5), polycystic ovarian syndrome (PCOS)(6), sleep and breathing disorders(7), Alzheimer's disease(8), cancers such as breast, prostate, and pancreas(9), The unifying concept is that all these patients are at a high risk of developing diabetes and CVD(10). CRP is synthesized by the liver(11) in response to factors released by fat cells (adipocytes).(12) It is a member of the pentraxin family of proteins.(11) It is not related to C-peptide or protein C. CRP was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C polysaccharide of pneumococcus.(13). Initially it was thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer(11), however discovery of hepatic synthesis demonstrated that it is a native protein.

The advantage of measuring CRP in the blood, rather than cytokines, is that the protein levels are much higher. Furthermore, CRP levels remain elevated for a longer period (days) than cytokines do; the latter may appear only transiently in the blood and thereby evade detection. The hs-CRP test can more accurately detect lower concentrations of the protein (it is more sensitive), which makes it more useful than the CRP test in predicting a healthy person's risk for cardiovascular disease. Arterial inflammation has emerged as central to the pathogenesis and clinical manifestation of atherosclerosis.

Furthermore, C-reactive protein (CRP), a nonspecific marker of inflammation, has been shown to predict outcomes in various atherosclerosis-related clinical situations(14). In fact, when the high-sensitivity hs CRP

assay is used, it appears to add prognostic information, even in patients who have low-density lipoprotein cholesterol (LDL-C) levels that are considered normal(15).

The idea that there is a close association between hs-CRP levels and the metabolic syndrome is easily understood, inasmuch as inflammation is closely linked to the metabolic syndrome itself, and cross-sectional studies have demonstrated a correlation between hs-CRP levels and all components of the NCEP ATP III definition of the metabolic syndrome. The extent to which elevated hs-CRP levels confer a worse prognosis among patients with the metabolic syndrome has been evaluated in several prospective studies(11).

The aim of the study

Is to assess the prevalence of increasing level of hsC.Reactive Protein among the patients with metabolic syndrome and its relation with atherosclerosis complication (IHD, CVA ,intermittent claudication).

Methods

A prospective cross-sectional study enrolled 84 male patients with metabolic syndrome, aged 40-70 years who attended the specialized center for endocrinology and diabetes in Baghdad -Alrisafa from November 2009 to March 2010.

Inclusion criteria;;considering the IDF(international Diabetes Federation) criteria which require presence of central obesity (waist circumference ≥ 80 for female and ≥ 94 for males)and two of the following: diabetes mellitus, impaired glucose tolerance, or impaired fasting glucose, blood pressure: $\geq 130/80$ mmHg or on anti-hypertensive medication, dyslipidemia: triglycerides (TG): ≥ 150 mg/dl and high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl .

Exclusion criteria;;patients with infection or inflammation,or chronic disease, patients with chronic kidney disease or chronic liver disease, and Patients taking medications with anti inflammatory action (steroid, NSAID, Statin).

Assessments were always between 8-10 am, patients were screened initially with a questionnaire for inclusion and exclusion criteria and about clinical evidence of atherosclerosis complication (IHD, CVA, Intermittent claudication) by clinical features (history and examination)

investigations (ECG, Echo study) for all and coronary angiography, Doppler study of lower limb and for carotid artery, brain CT scan if needed clinically. And for measuring hsCRP, the measurement method done by ELISA technique and the device type were (Bio Tek ELx800 Absorbance microplate). We consider hs-CRP level of more than 3mg/l a significant elevation (2). Middle aged considered below 60 years, older age are 60 years and above. Chi square test and T-test was used to assess significance of association between

comparable variables, P value of <0.05 regarded as significant.

Results:

Table 1 show that patients with metabolic syndrome and clinically diagnosed atherosclerosis had higher levels of hs-CRP than those with metabolic syndrome without clinical atherosclerosis which also show elevation, but to much lesser extent.

Table 1 hs-CRP relation to atherosclerosis

Groups	hs-CRP ≥3.0mg/l	hs-CRP < 3.0mg/l	Total
1-MS clinically complicated by atherosclerosis	30	5	35
2- MS clinically uncomplicated by atherosclerosis	30	19	49
Total	60	24	84
			p value=0.014

Table 2 show that mean hs-CRP is higher in patients with MS clinically had atherosclerotic complications than those with MS who had not with statistical significance.

Table 2 Mean hs-CRP level in MS patients with and without atherosclerosis

hs-CRP	Group 1	Group 2	p. value
Mean h.s.CRP value	6.04	4.92	0.048
S .D.	2.04	2.50	
Range of hs-CRP value	0.26-9.47	0.18-9.5	

Table 3 show that patients with MS and clinical atherosclerosis of middle age group had significant elevation of hs-CRP, while no significance found in those of old age.

Table 3 Relation of age to mean level of hs-CRP

age	Group 1		Group 2	P.value
Middle age <60	Number	10	11	0.007
	Mean	6.72	4.47	
	S.D.	2.83	2.58	
Elderly age ≥60	Number	25	38	0.29
	Mean	5.77	5.05	
	S.D.	2.7	2.49	

Table 4 show the results of the level of hs-CRP of MS patients how had hypertension with and without clinical atherosclerosis which reveal that patients with MS, hypertension and atherosclerosis had higher mean hs-CRP than those with MS and no hypertension.

Table 4 Relation of hypertension to hs-CRP level in both with atherosclerosis and without

Blood pressure	Group1		Group 2	p.value
Normal blood pressure patients	Number	10	27	0.58
	Mean	5.63	5.17	
	S.D.	2.23	2.3	
Hypertensive	Number	25	22	0.05
	Mean	6.2	4.61	
	S.D.	2.66	2.74	

Table5 show the relation of mean hs-CRP to waist circumference which reveal that there is a relation of higher level of hs-CRP to higher waist circumference.

Table 5 Relation of waist circumference to mean level of hs-CRP

Waist Circumference	GROUP 1		GROUP 2	P.VALUE
Normal	Number	9	23	0.49
	Mean	5.4	4.55	
	SD	1.1	1.21	
High	Number	26	26	0.05
	Mean	6.86	4.64	
	SD	1.23	1.12	

Table 6 show the relation of mean hs-CRP to body mass index (BMI) in both metabolic syndrome (MS) with and without atherosclerosis which is of no significance statistically for both.

Table 6 Relation of mean hs-CRP to BMI in atherosclerosis

BMI	GROUP 1		GROUP 2	P.VALUE
Less than 25	Number	9	13	0.39
	Mean	5.6	4.55	
	S.D.	2.3	2.38	
More than or =25	Number	26	36	0.08
	Mean	6.19	4.98	
	S.D.	2.64	2.63	

Discussion

As seen in table 1 the chance of having high reading of hsCRP ($\geq 3.0\text{mg/l}$) in patients with metabolic syndrome with complications is 6 times more than those with hs-CRP $< 3.0\text{mg/l}$ values ,while it is less than double in non complicated metabolic syndrome, with statistically significant p.value. and The summation table 1 show that the patients with metabolic syndrome with high reading of hsCRP are more than double of patient with metabolic syndrome with normal reading and this is consistent with other studies like wangtj(16)and Ford ES (17).

Table 2 revealed that the mean of hsCRP of complicated metabolic syndrome is higher than those without complication, with significant p.value, and this results was

consistent with many studies that show higher readings of hsCRP the higher risk of atherosclerosis(18,19) , as the inflammatory process is essential in the pathogenesis of atherosclerosis and this associated with the release of acute phase proteins as (hsCRP) , and these results also confirmed by other studies like wangtj(16)and Ford ES(17).

Table 3 show that mean of hsCRP in patients with complicated metabolic syndrome of middle age is higher than those without at the same age group , with significant p.value ,But the mean of hsCRP in patients with complicated metabolic syndrome of elderly age group are only mildly elevated compared to those without at the same age group , with insignificant p.value ,and these results was consistent with {Kenneth J. Krause} (20), and the possible explanation is that the

inflammation is more evident in middle age group than in old age (established atherosclerosis) , and also this could be explained by the fact that the old age patient have affected immune system (18),and the peak of inflammatory process of atherosclerosis occur in middle age and when patient reach older age fibrosis occur , so there is a benefit of measuring hsCRP in middle age with metabolic syndrome and suspicion of atherosclerosis more than in old age .

Table 4 revealed that the mean of hsCRP in hypertensive complicated metabolic syndrome is higher than those with hypertension and uncomplicated metabolic syndrome with significant p.value, But the mean of hsCRP in patients of normal blood pressure with complicated metabolic syndrome only mildly elevated than those without , with insignificant p.value. These were consistent with many studies (20) that showed that hypertension with metabolic syndrome and atherosclerosis led to increasing hsCRP level more than in non hypertension, it is also well known that hypertension is a risk factor for acceleration of atherosclerosis(21).

The results of table 5 show that the mean of hsCRP in patients with increasing waist circumference with complicated metabolic syndrome is higher than those of uncomplicated metabolic syndrome and same waist circumference, with significant p.value. But the mean of hsCRP in patients of normal waist circumference with complicated metabolic syndrome is mildly elevated than those without and have same waist circumference , with insignificant p.value. These were consistent with many studies(22), as the obesity types depends on the distribution of adipose tissue in different anatomic depots also has substantial implications for morbidity. Specifically, intra abdominal and abdominal subcutaneous fat(increasing in waist circumference) have more significance than subcutaneous fat present in the buttocks and lower extremities,and also well known association with complications of obesity, such as insulin resistance, diabetes, hypertension, dyslipidemia and all of these are components of metabolic syndrome with high risk of atherosclerosis ,so there is a benefit of measuring hsCRP in metabolic

syndrome patients who have central obesity(22).

The results in table 6 show that the mean of hsCRP in patients with increasing BMI ratio and complicated metabolic syndrome is higher than those with uncomplicated metabolic syndrome with same BMI but with insignificant p.value .and the mean of hsCRP in patients of normal BMI with complicated metabolic syndrome is mildly elevated than those without and same BMI , with insignificant p.valuealso,the possible explanation was that the BMI is not an accurate measurement of adipose tissue in the body (the obesity defined as a state of excess in adipose tissue mass) Although often viewed as equivalent to increased body weight, very muscular individuals may be overweight by numerical standards without having increased adiposity(22). There is increase in hsCRP in complicated patients more than uncomplicated but not as significant as with increasing waist circumference ,this study is not consistent with other studies(19) and this may be because we consider abnormal BMI value above 25 and other studies consider 30 as abnormal.

Conclusion

There is a great benefit of measuring hsCRP in patient with metabolic syndrome with suspicion of atherosclerosis specially in middle age group, hypertensive's and possibly in those with very high BMI and those with increase waist circumferenceas it is a strong marker of IHD in those patients.

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