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Original Research

Correlation between elevated hepatic enzymes & high-sensitivity CRP in metabolic syndrome

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Abstract

BACKGROUND AND OBJECTIVES: The phrase "metabolic syndrome" was used to describe the joint incidence of hyperlipoproteinemia, diabetes, hypertension, gout and obesity in combination with an increased incidence of cardiovascular disease, fatty liver and cholelithiasis. Chronic, sub-clinical inflammation and its association with Metabolic Syndrome are well documented.. Fatty liver is now believed to be an integral part of the metabolic syndrome, since it has been shown to be independently related to insulin resistance independent of obesity and abdominal adiposity.

AIM: to assess the status of high-sensitive C reactive protein and hepatic enzymes in patients' with Metabolic Syndrome.

METHODS: This study is a case-control study based on New National Cholesterol Education Programme Adult Treatment Panel III which approved the criteria of metabolic syndrome.

Forty-eight (48) patients (of both sexes) attending the Diabetic Consultant Clinic for follow up and monitoring therapy during the period from January, 2010 till the end of September, 2010; and forty-eight (48) apparently healthy volunteer that were comparable to patients group with respect to age and sex and serve as a control group were included in this study. They were screened for *Metabolic Syndrome criteria*: namely, high blood pressure, high body mass index, high fasting blood sugar, high triglyceride, low high density lipoprotein; a significant difference was found between patients and controls with respect to blood pressure, body mass index, fasting blood sugar, triglyceride, and high density lipoprotein (P<o.o5). For the two groups high-sensitive C reactive protein and hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, gamma glutammyl transferase and alkaline phosphatase) was measured using Enzyme Linked Immuno Sorbant Assay kit and colorimetric method respectively.

THE RESULTS: Blood pressure, body mass index were significantly higher in the Metabolic Syndrome than the control. Metabolic Syndrome group had significantly higher level of high-sensitive C reactive protein as well as higher level of hepatic enzymes than control group, ($p < 0.001$) and significantly higher levels of Low Density Lipoprotein-Cholesterol, triglyceride (TG), but lower High Density Lipoprotein-Cholesterol than the control group.Also high-sensitive C reactive protein showed a positive correlation with elevated hepatic enzymes ($p < 0.001$).

INCONCLUSION: Elevations in liver enzymes are correlated with higher serum concentrations of high-sensitive C reactive protein in Metabolic Syndrome

INTRODUCTION

Metabolic Syndrome (Met S) is an aggregation of conditions that together increases the risk of cardiovascular disease in individuals that would not otherwise be recognized to be at risk[1]. Additionally, Metabolic Syndrome increases the risk of developing diabetes mellitus and chronic kidney disease and is associated with a number of other disorders[1]. The phrase "metabolic syndrome" was used to describe the joint incidence of hyperlipoproteinemia, diabetes, hypertension, gout and obesity in combination with an increased incidence of cardiovascular disease, fatty liver and cholelithiasis[1].

It is a common, affecting approximately 24% of the adult U.S. population and dangerous[2], yet treatable risk factor for a variety of diseases, yet confusion about and rejection of the syndrome still exists. The lack of a consensus definition of Metabolic Syndrome, debate about its etiology and pathogenesis and lack of a consensus document for its treatment contribute to this confusion[2].

Chronic, sub-clinical inflammation and its association with Metabolic Syndrome is a well documented[3] Inflammatory mediators have been recognized as factors that increase the risk of cardiovascular disease, but also are one cause of insulin resistance[3]. Further, obesity has been associated with inflammation and more data is accumulating that obesity is a pro-inflammatory state[3].

Increased concentrations of inflammatory mediators, such as, C-reactive protein (CRP), tumor necrosis factor-alpha, interleukin-6 and others have been found in the obese[4]. Adipose tissue has been found to express most of these inflammatory markers[4].

Fatty liver is now believed to be an integral part of the metabolic syndrome, since it has been shown to be independently related to insulin resistance independent of obesity and abdominal adiposity. Non-Alcoholic Fatty Liver (NAFLD) associated biomarkers have indeed been correlated with metabolic syndrome, its components and cardiovascular disease[5].

The risk of having non-alcoholic steatohepatitis increases with the presence of components of Metabolic Syndrome. Liver markers have been shown to be associated with Metabolic Syndrome and predict Type-2 Diabetes Me

llietus.[7,8]

Further definitions have been proposed recently by various organizations or associations; for example, in Japan, the definition of MetS was determined in collaboration with eight Japanese medical societies in 2005.[9]

Thus, MetS using the criteria of New National Cholesterol Education Programme (NCEP), Adult Treatment Panel III (NCEP-ATP III), has been investigated for its possible relation to serum liver enzymes and CRP. To our knowledge, however, the associations of MetS with liver enzymes and CRP have not been fully investigated[9].

PATIENTS AND METHODS

This study is a case-control study based on New National Cholesterol Education Programme (NCEP), Adult Treatment Panel III which approved the criteria of metabolic syndrome.

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The approval of the institutional research ethics committee, and written consent of every patient included in the study were obtained.

The patients included in this study were 48 patients (of both sexes) aged 20-65 years; attending the Diabetic Consultant Clinic at Al-Kadhimiya Teaching Hospital for follow up and monitoring therapy during the period from January, 2010 till the end of September, 2010.

They were screened for *Met S. criteria*:

The study included another 48 apparently healthy volunteer that were matched to patients group with respect to age and sex and serve as a control group.

Inclusion and Exclusion Criteria:-

The following inclusion criteria were used:

1- Adults (≥ 20 years)

2- Only type 2 diabetes.

While exclusion criteria were the following:

1- Type 1 diabetes.
2- Age less than 20
3- Gestational diabetes.
4- Chronic alcoholism.
5- Presence of chronic hepatitis B or C on serology.

Five milliliters of fasting venous blood were withdrawn from each patient, in supine position, without application of tourniquet. Samples were transferred into clean new plane tube, left at room temperature for 15 minutes for clotting, centrifuged, and the separated serum was divided into two parts and stored at –20^{o} C until analysis of high-sensitive CRP (hs-CRP)[10] and hepatic enzymes, which was done within one month after collection. [11]

Serum high-sensitive CRP was measured using ELISA kit DRG CRP, HS (C-Reactive Protein) (EIA-3954). DRG International Inc., USA. www.drg-international.com.

Liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase(AST), gamma glutammyl transferase (GGT) and alkaline phosphataseALP) were determined by colorimetric method [11] using suitable enzymatic kit: Alkaline phosphatase (ALP) (BioMerieux ® Sa France), Gamma –GT / SOLUBLE GPNA (BIOLABO REAGENTS) 02160 Maizy ,France; AST/GOT and ALT/GPT ((BIOLABO REAGENTS) 02160 Maizy, France).

Statistical analysis was done using Excel system version 2003. When P-value was less than 0.05, the difference is considered statistically significant.

RESULTS:

For Met S group: the *fasting blood sugar (FBS)* ranges between 5.7-22 mmol/L (mean FBS ± SD = **10.99+4.47** mmol/L); the *triglyceride* ranges between 1.4-5 mmol/L (mean TG ± SD = **3.48±1.02** mmol/L); the *high-density lipoprotein (HDL)* ranges between 0.56-1.1 mmol/L (mean HDL ± SD = 0.94+0.18 mmol/L); the *LDL size Index (LDL-SI) (molar ratio between TG : HDL)* ranges between (2- 8.56)(Mean LDL_SI ± SD = **3.84±1.49**); the *body mass index (BMI)* ranges between 27-41 kg/m^2 (mean BMI ± SD = **33.75±4.86**Kg/m^2); the *systolic blood pressure* ranges between (120-170) mmHg (mean BP ± SD = 147.9 ± 11.5 mmHg); the *diastolic blood pressure* ranges between (80-100) mmHg (mean BP ± SD = 89.4 ± 6.4mmHg) as in Table 1.

For control group: the *fasting blood sugar (FBS)* ranges between 4.2-6 mmol/L (mean FBS ± SD = 5.03+0.47mmol/L); the *triglyceride* ranges between(0.4-2.5)mmol/L (mean TG ± SD = 1.56+0.74 mmol/L); the *high-density lipoprotein (HDL)* ranges between 4.03+0.47 mmol/L (mean HDL ± SD = 1.32+0.33 mmol/L) ; The *LDL size Index (LDL-SI)(ratio between TG : HDL)* ranges between (0.4-3.4)(mean LDL-SI ± SD = 1.34+0.80);the *body mass index (BMI)* ranges between 20-23 kg/m^2 (mean BMI ± SD = **21.68 ±0.74**Kg/m^2); the systolic blood pressure ranges between(110-120) mmHg (mean BP ± SD = 111.6 ± 5.7 mmHg); the diastolic blood pressure ranges between 70-80 mmHg (mean BP ± SD = 75.1 ± 4.1mmHg) as in Table 1. A significant difference was found between patients and controls with respect to FBS, BMI, TG, HDL and BP (P<0.001) as in **Table 1.** Serum high-sensitive CRP and hepatic enzymes were significantly elevated in patients with MetS compared with controls [P < 0.001] as in **Table 2**.

Table 1. Criteria for studied groups (patients vs control) presented as mean + SD.

Variable	G1	G2	P-value
BMI(Kg/m^2)	33.5 ± 5.1	21.7 ± 0.7	0.004
SBP(mmHg)	147.9 ± 11.9	111.6±5.7	0.0004
DBP(mmHg)	89.4 ± 6.4	75.1±4.1	0.007
FBS(mmol/L)	11 ± 4.5	5.03±0.47	0.005
TG(mmol/L)	3.48±1.02	1.56±0.74	0.0045
HDL(mmol/L)	0.94± 0.18	1.32±0.33	0.0054
LDL-SI	3.84±1.49	1.3 ± 0.8	**0.006**

Table 2. The mean serum level of high sensitivity CRP & hepatic enzymes in patients with metabolic syndrome versus control groups (presented as mean + SD).

Variable	G1	G2	P-value
Serum hs-CRP (mg/L)	11.11 ± 3.25	0.48 ± 0.28	0.004
Serum ALT (IU/L)	49 ± 12.6	20 ± 6.2	0.01
Serum AST (IU/L)	34.9 ± 5.9	21.7 5.7	0.003
Serum GGT (IU/L)	51.6 ± 14	17.6 ± 3.5	0.0015
Serum ALP (IU/L)	70.7 ± 13.5	44.37 ± 9.9	0.009

(G1): Metabolic Syndrome Patients.

(G2): Apparently healthy Control Subjects.

A significant positive correlation was found between hs-CRP and ALT, AST, GGT and ALP (r=0.8, P<0.001; r=0.6, P<0.001; r=0.6, P<0.001; r=0.8, P<0.001) in patients with MS as in Figure 1,2 3, 4; however, this correlation was lost in control group

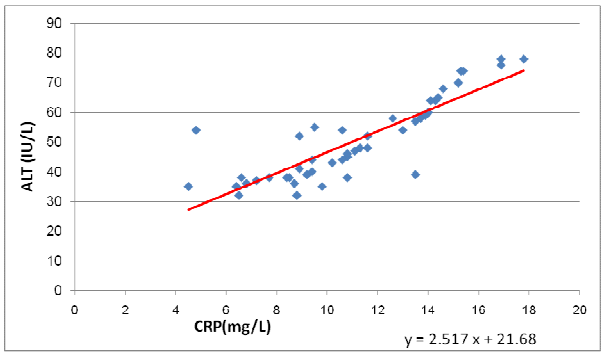

Figure 1. Correlation between serum hs-CRP & ALT in G1: Metabolic Syndrome patients. (n=48; r = 0.84; P< 0.001).

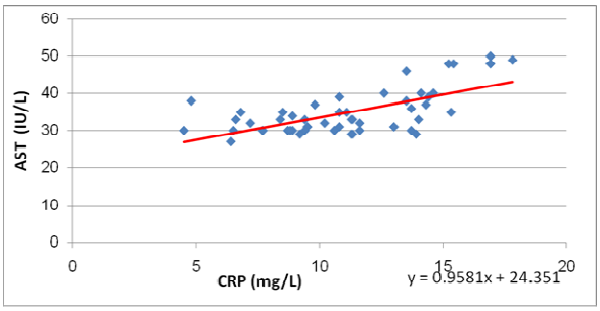

Figure 2. Correlation between serum hs-CRP & AST in G1: Metabolic Syndrome patients. (n=48; r = 0.64; P< 0.001).

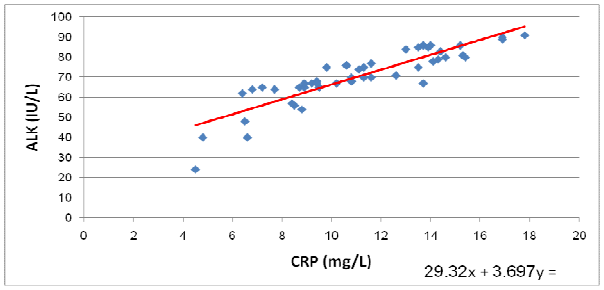

Figure 3. Correlation between serum hs-CRP & ALP in G1: Metabolic Syndrome patients. (n=48; r = 0.87; P< 0.001).

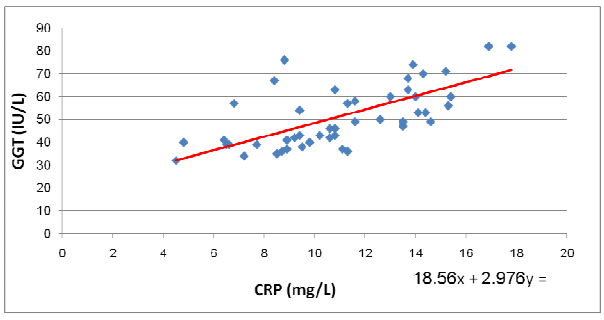

Figure 4. Correlation between serum hs-CRP & γ-GT in G1: Metabolic Syndrome patients. (n=48; r = 0.84; P< 0.001).

DISCUSSION:

In this study, a representative sample of adult males and females without any clinical evidence of cardiovascular or other chronic disease was studied, and the fact that the MetS was related with a liver marker, like GGT, AST, ALT and ALP was found[12,13].

Moreover, AST, ALT or GGT, as a marker of the syndrome were taken into account, and this denoting to aminotransferases levels should not be considered together when evaluating the development of the metabolic syndrome but should be considered with other liver enzyme together.[12,13]

Additionally, in this study, there was a significant increase in serum levels of liver enzymes in patients with metabolic syndrome.

And one of the most common causes of mild to moderate elevations of these liver tests is a condition called fatty liver. Causes of fatty liver include diabetes mellitus and obesity.[14, 15]

In insulin resistance (IR) study show that liver enzymes may predict to MetS and additionally, not only ALT but ALT /AST ratio also may be used as a marker for MetS[16]

Similar reports of elevated liver enzymes level have been reported in patients with MetS.[17, 18]

ALT and GGT has the Major role of liver enzymes which has been related with hepatic fat deposition and IR which plays a major role in MetS.[18]

The rise in the liver enzymes level could be attributed to excessive liver damage in Met S patients.[19]

Furthermore, hepatic enzymes (AST, ALT, and GGT) have linked to cardiovascular Disease (CVD) and MetS[20] through the significant positive correlation between hepatic enzymes and hsCRP which was found in this study.

Also, the importance role of liver function tests, especially ALT and GGT in diagnosis of MetS[20] was observed in this study.

GGT is central in glutathione hemostasis that is an important antioxidant defense for the cell. Therefore, GGT plays an important role in antioxidant defense systems Elevated GGT levels could be a marker of oxidative stress and subclinical inflammation.GGT adsorbs onto circulating (LDL-C) and can catalyze its oxidation[21].

In addition, several Parallel evidence from epidemiological studies suggests that higher serum GGT concentration was associated with development of (CVD) risk factors[22], and independent risk factor for the development of diabetes mellitus[23], stroke and

hypertension ,dyslipidemia, and when raised with other liver enzymes in the metabolic syndrome ,that may be useful in Metabolic Syndrome diagnosis[23].

In this aspect they may have a predictive value in diagnosis of Metabolic Syndrome[24].

CONCLUSION

With respect to our clinical observations, we hypothesize that high liver function tests, especially ALT and GGT levels, are associated with Metabolic Syndrome and correlate positively with novel cardiovascular risk factors such as (CRP) in this aspect they may have a predictive value in diagnosis of Metabolic Syndrome

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