Relationship between Elevated Liver Enzymes and Metabolic Syndrome among Egyptian Adults

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Background and study aim: Liver enzymes are important markers for hepatocyte damage. Metabolic syndrome (MS) is a combination of metabolic abnormalities including high blood glucose, obesity, hypertension and dyslipidemia. The incidence of MS is believed to be increasing in Egypt. The purpose of this study is to examine the relationship between elevated liver enzymes and MS among Egyptian adults.

Patients and Methods: A total 138 apparently healthy subjects were randomly included (99 females and 39 males). Demographic, clinical (blood pressure, body mass index and waist circumference) and biochemical (measurements of alanine aminotransferase (ALT), aspartate amino-transferase (AST), alkaline phosphatase (ALP), lipid profile, blood glucose and viral markers) were collected from every subject. Metabolic syndrome was defined according to a well-known criteria and subjects in the final analysis were divided into group I; metabolic syndrome and group II; non-metabolic syndrome subjects.

Results: In this study, 92 persons fulfilled three of the five criteria of metabolic syndrome (group I) with prevalence of 66.7% while group II (non-metabolic syndrome) represented 33.3%. Patients with MS were older and less physically active in comparison with group II. There were an association between elevations in liver enzymes (ALT, AST, ALP) and MS. ALT, AST and ALP were elevated in 42.4%, 17.2% and 20.7% of patients with MS respectively. ALT and AST showed positive correlation with elevated blood glucose and triglycerides levels while AST/ALT ratio showed negative correlation with diastolic blood pressure, triglycerides level and waist circumference. The more items of MS the patient have the higher the level of liver enzymes.

Conclusion: Among Egyptian adults elevated levels of liver enzymes were associated with MS and a correlation was noticed with its components.

INTRODUCTION

Liver enzymes are important markers for liver damage and are measured in the blood as a reflection of the occurrence and sometimes the severity of this damage, although its level is sometimes affected by non-hepatic medical conditions e.g. stroke, sarcopenia **[1,2]**.

Metabolic syndrome (MS) is a condition associated with metabolic abnormalities that are characterized by central obesity (e.g. waist circumference or body mass index), hypertension (e.g. systolic or diastolic blood pressure), hyperglycemia (e.g. fasting plasma glucose) and dys-lipidemia (e.g. triglyceride and high-density lipoprotein cholesterol) **[3]** and was found to be a major risk factor for cardiovascular diseases and diabetes **[4]**.

The incidence of metabolic syndrome is believed to be increasing in Egypt depending on the high prevalence rate of obesity (30.3%) reported by the 2010 WHO report **[5,6]**.

The prevalence of non-alcoholic fatty liver disease (NAFLD) varies across the studies ranging from 30-40% in men to 15-20% in women, while the prevalence of NAFLD sharply rises to 70% in people with MS and type 2 diabetes (T2DM). The natural history

of NAFLD begin with steatosis (accumulation of fat in hepatocyte) then inflammation (steatohepatitis) and may progress to liver fibrosis and end with cirrhosis. This sequence has been proposed to occur among patients with MS **[7,8]**.

The relationship between MS and elevated liver enzymes was not studies extensively in the Egyptian literature. Consequently, we carried out this study enrolling adult populations to study the relationship between liver enzymes and metabolic syndrome.

PATIENTS AND METHODS

During 12-month period from august 2017 to August 2018, this cross sectional multi-center study was carried out. A total of 138 apparently healthy subjects (99 females, 39 males) were included. Their ages ranged between 19-47 years. All subjects were randomly picked up from the gym fitness halls and investigated for: History taking, determination of waist circumference, weight and height and blood pressure. On the next day, the overnight fasting subjects gave informed verbal and written consents followed by blood sample withdrawal under complete aseptic precautions for determination of blood lipids, blood glucose and liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), HCV antibody and HBs Ag.

Inclusion criteria:
Adult patients, both sexes, patients willing to participate

Exclusion criteria:
Known cases of diabetes, hypertension, dyslipedamia, drug abusers, any chronic medical disease e.g. fatty liver, NAFLD and chronic hepatitis of any cause, liver cirrhosis, renal impairment, any drug that may affect the level of liver enzymes e.g. statins, fibrates

Definitions:

- **Criteria of Metabolic Syndrome** (MS): Was defined if the person had at least three of the following criteria following the unified criteria published in the National Cholesterol Education Program Adult Treatment Panel III guidelines **[9]**. These include the following: (1) abdominal obesity, defined as waist circumference ≥90 cm (40 inch) for men and ≥85 cm for women (35) inch (2) fasting blood glucose levels ≥110 mg/dL; (3) triglycerides (TG) ≥150 mg/dL; (4) high-density lipoprotein (HDL) cholesterol <40 mg/dL for men, and <50 mg/dL for women; and (5) hypertension, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg.
- **Waist circumference** was measured at the midpoint between the lower costal margin and the upper margin of iliac crest using a tape measure.
- **Height:** was determined while the bear footed person stands up straight besides the scale
- **Blood pressure** was measured three times after 5 min rest using a mercury sphygmomanometer and the average of the last two measurements was used **[10]**.
- **Elevated serum ALT or AST levels** were defined in this study as greater than 40 U/L.

Statistical Analysis
Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test or Mann Whitney, multiple by ANOVA or Kruskal Wallis, correlation by Pearson's correlation or Spearman's. P value was set at <0.05 for significant results & <0.001 for high significant result. In the final analysis patients were divided into 2 groups. Group I; were patients who fulfilled three criteria to define MS. Group II; were patients who did not fulfill three criteria to define MS.

Ethical Considerations
The study was conducted in concordance with human rights and declaration of Helsinki. All patients gave verbal and written informed consents for participating in the study and for performing all relevant interventions. Subjects were informed that they could withdraw at any time.

RESULTS

Study populations

This study comprised a total of 138 of subjects of them 99 were females (71.7%) and 39 were males (28.3%) and their ages ranged between 19 and 47 years. There were no dropouts from the final analysis. Regarding the comparison between both groups, patients with MS (group I) were significantly older than group II (P 0.002). Prevalence of smoking among study populations represented 60.1% but without significant difference between both groups similar to the occupation. However, patients with MS were physically inactive and lazy to exercise in comparison to group II (P 0.02) (Table 1).

Prevalence of Metabolic syndrome

In this study 92 person fulfilled three of the five criteria of metabolic syndrome with prevalence of 66.7% while group II represented 33.3% (Figure 1). When individual parameters of MS were calculated a total of 93(66.4%), 82(59.4%), 79 (57.2%), 57(41.3%) and 52 (37.7%) subjects had abnormality in waist circumference, high triglycerides level, low HDL, high fasting blood glucose and high blood pressure in order of frequency respectively. This means that almost always our patients with MS had abnormality in their waist circumference (central obesity).

Association between liver enzymes and metabolic syndrome

In the current study there were significant associations between the abnormally high levels of liver enzymes (ALT, AST, ALP, AST/ALT ratio) and metabolic syndrome (Table 2).

The prevalence elevated ALT in subjects with MS was 42.4%. The prevalence of the components of MS in subjects with elevated ALT were as follow; 39% with high blood pressure, 56.1% with high fasting blood sugar, 61% with high TG, 68.3% with low HDL cholesterol, 68.3% with abdominal obesity. Elevated levels of ALT is significantly associated with high fasting blood glucose and high triglycerides levels with P values of 0.022 and 0.002 respectively.

The prevalence of elevated AST in subjects with MS was 17.2%. The prevalence of the components of MS in subjects with elevated AST were as follow; 44% with high blood pressure, 52% with high fasting blood sugar, 60% with high TG,72% with low HDL cholesterol, 72% with abdominal obesity. Elevated levels of AST is significantly associated with high triglycerides level with P value of 0.029.

The prevalence of elevated ALP in subjects with MS was 20.7%, the prevalence of the components of MS in subjects with elevated ALT were as follow; 37.7% with high blood pressure, 46.4% with high fasting blood sugar, 53.6% with high TG,67.9% with low HDL cholesterol, 64.3% with abdominal obesity (Table 3).

Correlation between liver enzymes and components of metabolic syndrome

When the levels of liver enzymes were correlated with different components of MS there were different patterns of correlations. Alkaline phosphatase showed positive correlation with systolic blood pressure. ALT showed positive correlation with fasting blood sugar, triglycerides levels, waist circumference and BMI. AST showed positive correlation with waist circumference and BMI and showed negative correlation with low HDL level. However, AST/ALT ratio was positively correlated with low HDL level and negatively correlated with diastolic blood pressure, triglycerides level and waist circumference (Table 4). This means that markers of hepatocyte injury (ALT, AST) are correlated with components of MS rather than markers of cholestasis (ALP). It is also noticeable that the levels of liver enzymes are getting higher when the subjects had more components of MS (supplementary material).

Table 1: Baseline characteristics of both groups

	Group I (N=92)	Group II (N=46)	Total	P
Age (Years)	**49.41**±10.63	**43.23±11.998**		**0.002***
Sex				
Females	69 75.0%	30 65.3%	99 71.7%	0.22
Males	23 25.0%	16 34.7%	39 28.3%	
Smoking				
Active	58 63.0%	25 54.4%	83 60.1%	0.32
Non-smoker	34 37.0%	21 45.6%	55 39.9%	
Physical activity				
Not done	50 54.3%	16 34.7%	66 47.8%	
Infrequent	35 38.0%	20 43.4%	55 39.8%	0.02*
Regular	7 7.7%	10 21.9%	17 12.4%	
Occupation				
Yes	78 84.7%	38 82.6%	116 84.1%	0.74
No	14 15.3%	8 17.4%	22 15.9%	

*** Significant**

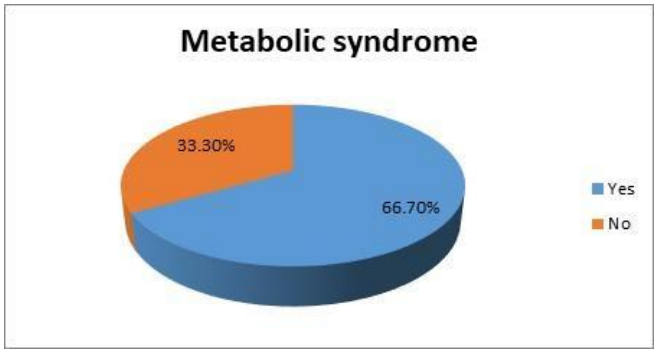

Figure 1: Prevalence of Metabolic syndrome among study subjects

Table 2: Mean level of Liver enzymes in the two groups

	Group I (N=92)	Group II (N=46)	P
ALP (IU)			
Mean±SD	83.59±25.5	74.19±26.3	0.03*
Normal N (%)	66 (71.7%)	44 (95.7%	0.0009**
High N (%)	26 (20.7%)	2 (4.3)	
ALT (IU)			
Mean±SD	57.92±17.71	42.54±18.1	0.00**
Normal N (%)	53 (57.6%)	44 (95.7%)	0.00**
High N (%)	39 (42.4%)	2 (4.3%)	
AST(IU)			
Mean±SD	39.39±13.6	30.6±14.2	0.0001**
Normal N (%)	67 (72.8)	44 (100%)	0.0002**
High N (%)	25 (17.2%)	0 (0%)	
Ratio of AST/ALT	**0.58**±0.21	**0.79±0.2**	**0.00****

*** Significant, ** Highly significant**

Table 3: Levels of ALT, AST and ALP in relation to components of metabolic syndrome

		ALT			AST			ALP		
		Normal	High	Total	Normal	High	Total	Normal	High	Total
BP	Normal (N/%)	61 (62.9%)	25 (61.0%)	86 (62.3%)	72 (63.7%)	14 (56.0%)	86 (62.3%)	70 (63.6%)	16 (57.1%)	86 (62.3%)
	High (N/%)	36 (37.1%)	16 (39.0%)	52 (37.7%)	41 (36.3%)	11 (44.0%)	52 (37.7%)	40 (36.4%)	12 (42.9%)	52 (37.7%)
	P	0.83			0.47			0.52		
FBS	Normal (N/%)	63 (64.9%)	18 (43.9%)	81 (58.7%)	69 (61.1%)	12 (48.0%)	81 (58.7%)	66 (60.0%)	15 (53.6%)	81 (58.7%)
	High (N/%)	34 (35.1%)	23 (56.1%)	57 (41.3%)	44 (38.9%)	13 (52.0%)	57 (41.3%)	44 (40.0%)	13 (46.4%)	57 (41.3%)
	P	0.022*			0.23			0.53		
TG	Normal (N/%)	66 (68.0%)	16 (39.0%)	82 (59.4%)	72 (63.7%)	10 (40.0%)	82 (59.4%)	69 (62.7%)	13 (46.4%)	82 (59.4%)
	High (N/%)	31 (32.0%)	25 (61.0%)	56 (40.6%)	41 (36.3%)	15 (60.0%)	56 (40.6%)	41 (37.3%)	15 (53.6%)	56 (40.6%)
	P	0.022*			0.029*			0.117		
HDL	Normal (N/%)	46 (47.4%)	13 (31.7%)	59 (42.8%)	52 (46.0%)	7 (28.0%)	59 (42.8%)	50 (45.5%)	9 (32.1%)	59 (42.8%)
	Low (N/%)	51 (52.6%)	28 (68.3%)	79 (57.2%)	61 (54.0%)	18 (72.0%)	79 (57.2%)	60 (54.5%)	19 (67.9%)	79 (57.2%)
	P	0.08			0.09			0.204		
Abdominal obesity	No (N/%)	32 (33.0%)	13 (31.7%)	45 (32.6%)	38 (33.6%)	7 (28.0%)	45 (32.6%)	35 (31.8%)	10 (35.7%)	45 (32.6%)
	Yes (N/%)	65 (67.0%)	28 (68.3%)	93 (67.4%)	75 (66.4%)	18 (72.0%)	93 (67.4%)	75 (68.2%)	18 (64.3%)	93 (67.4%)
	P	0.88			0.58			0.69		
Total (100%)	(N)	97	41	138		25	138	110	28	138

Table 4: Correlation between Liver enzymes and components of metabolic syndrome

		ALP	SGPT	SGOT	AST/ALT RATIO
SBP	r	.217*	.148	-.003-	-.155-
	P	.011	.083	.973	.070
	N	138	138	138	138
DBP	r	-.009-	-.021-	-.112-	-.176-*
	P	.914	.807	.191	.039
	N	138	138	138	138
FBS	r	.110	.225**	.095	-.109-
	P	.198	.008	.270	.205
	N	138	138	138	138
TRIG	r	.146	.317**	.155	-.199-*
	P	.087	.000	.070	.019
	N	138	138	138	138
HDL	r	-.107-	-.162-	-.346-**	.168*
	P	.212	.058	0.00	.049
	N	138	138	138	138
WC	R	.022	.425**	.412**	.320
	P	.801	0.00	0.00	-.001**
	N	138	138	138	138
BMI	R	-.020-	.451**	0.419**	.154
	P	.816	0.00	0.00	.071
	N	138	138	138	138

DISCUSSION

The relation between liver enzymes and metabolic syndrome has not been investigated among Egyptian patients so far. Furthermore, the daily medical practice in Egypt incorporates liver enzymes particularly ALT and AST in the routine labs. Depending on its simplicity, affordable price and reproducibility liver enzymes estimation may be of value to predict MS if found to have significant association with these metabolic derangements.

The prevalence of MS in this study is surprisingly high (66.7%) when compared for prevalence rates from other areas around the globe. The following prevalence rates of 26.9%, 42.1%, 39.9%, 33% have been reported among Korean **[10]**, Egyptian **[11]**, Saudi **[12]**, USA **[13]** populations respectively.

But the question is, why the prevalence rates are higher in this study in comparison to others? and the answer is that most of the other studies included adult patients performing regular health checkup or used the national databases of adults while in Egypt we lack both services and in the current study we picked up our patients from the gym fitness halls. Usually patients attend these fitness halls for weight reductions and improve their athletic status presumably they are not diseased. Furthermore, we excluded patients with chronic diseases or drug users from the current study to avoid any impact on the study parameters.

The quiet high prevalence rate of MS in this study is believed to be parallel to the high prevalence rates of obesity reported by WHO in 2010 to be 30.3% among Egyptian subjects. Furthermore, recently a nationwide screening program for HCV and non-communicable diseases including obesity is being conducted and preliminary results points to very high prevalence rates of obesity even doubles the WHO figures (data not yet published). In favor of these facts is the finding that all patients in group I had abnormal waist circumference, similar results were reported from Suez Canal region in the East of Egypt by Fathi et al. **[11]**.

For demographics, there were significant associations between MS and subjects' age and lack of physical activities. Similar findings were found also among Korean **[10]** and Thai populations **[14]**.

To reach meaningful conclusions from our study we will answer two questions. First, is there an association between liver enzymes and MS among our study subjects? Second, if there is an association is there any correlation between increasing levels of serum liver enzymes and different components of MS.

From the data presented, there was an association between the increases in liver enzymes (ALT, AST and ALP) and metabolic syndrome when compared with adults not fulfilling the diagnostic criteria of MS. ALT, AST and ALP were elevated in 42.4%, 17.2% and 20.7% of patients with MS respectively. Similar results were reported from other geographic regions. Kim and Han **[10]** evaluated the association between ALT and AST and MS in 11,587 Korean population and they found that elevated levels of ALT and AST, even within the normal range **[15,16]**, were associated with prevalence of MS. Among Thai populations Perera1 et al. **[14]**, found that increased liver marker (ALT, AST, and ALP) concentrations are associated with an increased MS risk. They noticed not only positive linear correlation with MS but also with the increasing number of the MS components, we reported the same findings in this study.

Correlation between elevated liver enzymes and components of MS showed that enzymes of hepatocellular injury (ALT, AST, AST/ALT ratio) rather than cholestatic enzymes (ALP) had correlations with individual components of MS. ALT significantly correlated with the increase in blood sugar, hypertriglceridamia, increase abdominal obesity and increase body mass index while AST significantly correlated with the decrease in HDL, increased abdominal obesity and the increase in body mass index.

A question pops up. What is the mechanism beyond elevation of liver enzymes among patients with MS. It seems that accumulation of fat in hepatocyte is associated **[17,18]** with picture of NAFLD particularly with hypertriglyceridemia, diabetes and obesity results in hepatocyte oxidative stress and injury and a sort of inflammation within the liver tissue **[19]** and in our study these conclusions were reinforced by higher prevalence of MS (42.4%) among subjects with elevated ALT (the most specific liver enzyme) when compared with AST and ALP. This have been also reported in some studies **[14,20-22]**. Patel et al. **[23]** showed that increase visceral fat accumulation, elevated liver enzymes and MS were associated with NAFLD and hepatic insulin resistance. In another study Malk et al. **[24]** found that most of NAFLD

patients were insulin resistant with central obesity and impaired glucose tolerance.

Another explanation for the elevated liver enzymes is related to the increase of visceral fat accumulation which stimulate hepatic lipogenesis and triglyceride-rich lipoprotein secretion. Also, central obesity increase secretion of proinflammatory adipocyto-kines and decreased anti-inflammatory adiponectin an insulin-sensitizing that increase insulin resistance and oxidative stress which associated with increase liver enzymes **[23]**.

This study had some potential limitations. First, absence of objective measurement of liver tissue such as ultrasonography or biopsy to determine the presence and degree of steatosis, inflammation, and fibrosis. When we planned for this study it was clear in our minds that we are alarming many physicians including primary health care givers, non-specialists and specialists about the value of liver enzymes in relation to MS and its components while ultrasonography and liver biopsy are only practiced by specialists and not routinely performed in our daily medical practice as do the measurements of liver enzymes. Second, the small number of patients in this study. We were careful that many confounder may affect the serum levels of liver enzymes e.g. viral and drug induced hepatitis that is not uncommon in our community and that is why we excluded patients taking any chronic medications and patients with chronic diseases e.g. diabetes, hypertension, hyperlipidemia and we performed viral markers for all patients together with careful history taking

This is first, to the best of our knowledge, study to examine the association between liver enzymes and MS in Egyptian people. We think it would be of value particularly with the increasing prevalence rates of obesity among our population and consequently rates of MS as well **[21]**.

In conclusion, elevated liver enzymes are associated with MS and correlated with many components of MS and its measurements could be used as non-invasive, simple and reproducible in the early diagnosis MS in the daily medical practice. Further studies to determine predictive value of liver enzymes in metabolic syndrome related cardiovascular disease and type 2 diabetes are warranted.

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