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SERUM HEART TYPE FATTY ACID BINDING PROTEIN (H-FABP) LEVELS IN METABOLIC SYNDROME

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ABSTRACT: Background: Metabolic syndrome (MetS) is a defined cluster of cardiometabolic abnormalities that increases an individual's risk of type2 diabetes (T2D) and cardiovascular disease (CVD). Heart fatty acid binding protein (H-FABP) is a major cytoplasmic low-molecular weight protein and released into the circulation when the myocardium is injured. Previous studies have demonstrated that H-FABP is closely associated with acute coronary syndrome, hypertrophic and dilated cardiomyopathy, heart failure, stroke, obstructive sleep apnea syndrome, pulmonary embolism. The aim of this study was to investigate serum H-FABP value in the patients with MetS. **Methods:** We measured serum H-FABP levels in 209 adult Tunisian MetS patients (108 diabetic MetS and 101 non-diabetic MetS) matched by gender and ethnic origin and 193 control subjects, using immunoturbidimetric method. All subjects underwent anthropometric and biochemical examinations. **Results:** Serum H-FABP levels were significantly higher in patients with MetS than in control subjects 9.80±4.75 and 3.78±1.04 ng/ml, respectively, (P<0.001). Serum H-FABP levels were significantly higher in patients with diabetic MetS than in without diabetic MetS, 12.63±4.92 and 6.77±1.80 ng/ml, respectively, (P<0,001). There were statistically significant differences between patients without diabetic MetS and control subjects, 6.77±1.80 and 3.78±1.04 ng/ml, respectively, (P<0.001). H-FABP was correlated with cardio metabolic parameters and insulin resistance. **Conclusion:** Patients with MetS have an increased risk of death from cardiovascular diseases. H-FABP seems to be a marker that will enable the detection of cardiac injury in the early asymptomatic period in patients with MetS.

INTRODUCTION: The National Cholesterol Education Program's Adult Treatment Panel III report (NCEP-ATP III) identified the metabolic syndrome (MetS) as a multiplex anthropological and biochemical abnormalities including Lipid disorder, obesity, diabetes in general and high blood pressure [1, 2].

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MetS is associated with an increased risk for the development of type2 diabetes (T2D), coronaty heart disease (CHD), and cardiovascular disease (CVD) [3]. On the other hand, T2D has atherosclerotic as well as microvascular changes as chronic complications and is also recognized as an independent risk factor for CVD [4, 5].

Since the initial discovery of FABPs in 1972, at least nine members have been identified. The family contains liver (L-), intestinal (I-), heart (H-), adipocyte (A-), epidermal (E-), ileal (Il-), brain (B), myelin (M-) and testis (T-) FABPs [6]. Human heart-type fatty acid binding protein (H-FABP) is a 15

kDa small protein consisting of 132 amino acids [7]. H-FABP is abundant in the cytosol of cardiomyocytes, constituting 5–15 % of the cytosolic protein pool [8], and transports fatty acids in these cells. It is a powerful regulator of the mitochondrial beta-oxidative system in the heart [9]. It was first noted to be a marker of myocardial infarction (MI) in 1988 [10-11], it is rapidly released from the cytosol into the circulation after myocardial ischemia and necrosis [12]. H-FABP was shown to be associated with chronic heart failure patients [13].

Although, major cardiovascular events are the first clinical manifestation of coronary artery disease (CAD) in more than half of individuals, these acute coronary events occur after long preceding periods of subclinical disease development [14]. Therefore, H-FABP has been used diagnostic marker for acute coronary syndromes [15]. On the other hand, previous studies have demonstrated that serum level of H-FABP is increased in patients with hypertrophic and dilated cardiomyopathy, heart failure, stroke, obstructive sleep apnea syndrome and pulmonary embolism [13-21].

In the present study, we tested the hypothesis that serum H-FABP level is detectable in the circulation of patients with MetS. Elevated circulating levels of H-FABP may be a marker that will enable the detection of cardiac injury in the early asymptomatic period in patients with MetS.

MATERIAL AND METHODS:

Subjects: This is a prospective study, in which sampling was carried between January and September 2014. All participants gave written informed consent and the Hospital's Ethics Committee approved the study protocol.

The study is based on two types of populations recruited from intermediate group of basic health Sousse Tunisia: a control population and population with MetS. The healthy subjects, recruited to attend for a routine check-up (in the same time of patients recruitment), included 31 male and 162 females, with a mean age of 58±12.5 years and 48.82±9.66 years, respectively. Those with medical illnesses such as acute infection, chronic renal failure, malignancies, and other severe medical illnesses were excluded from the enrollment. Alcohol intake, smoking habits, medication history, and medical history, at the time of coronary angiograms, were obtained by the chart review and from the self-questionnaire.

The patients included 57 males and 152 females, with a mean age of 60.11±10.71 years and 58.48±10.83 years, respectively. This patients group consisted on 108 diabetic MetS and 101 non diabetic MetS.

MetS and metabolic risks are defined according to the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) guidelines. MetS was defined as having at least three of the following metabolic risk factors:

- Central obesity (waist circumference (WC) > 88 cm in women, > 102 cm in men);
- Hypertriglyceridemia (fasting triglycerides ≥ 1,7 mmol/l (1,50 g/l));
- Low high-density lipoprotein (HDL) cholesterol (fasting HDL <1.29 mmol/l (0,50 g/l) in women, < 1,03 mmol/l (0,40 g/l));
- Glucose intolerance (fasting glucose ≥.6,1 mmol/l (1,10 g/l));
- Hypertension (sitting blood pressure ≥130/85 mmHg obtained as a mean of two readings taken after resting for at least 10 min or on regular antihypertensive medications).

Measurements: Height, weight, systolic, and diastolic blood pressures were measured in duplicate and the results were averaged. Weight height and waist circumference were measured. The body mass index (BMI) was calculated by dividing the weight (kg) with the square of height (m).

All blood samples were obtained after overnight fasting. Fasting blood glucose, urea and creatinine were measured from fluoride plasma. Total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ɤ-glutamyltransferase (ɤGT) and free fatty acids (FFA) were measured. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation: [LDL-C (mmol/l) = CT – (TG / 2.2 + HDL-C)].

Serum insulin was determined with a microparticle enzyme immunoassay. The insulin resistance index estimated by the homeostasis model assessment method (Homeostasis Model Assessment – Insulin Resistance (HOMA-IR)) was calculated as follows: [fasting serum insulin (µU /ml) x fasting plasma glucose (mmol/l)/22.5].

Those patients were well controlled in terms of glycosylated hemoglobin (HbA1c) determined by a latex agglutination immunoassay type TINIA (turbidimetric inhibition immunoassay) by automate (Randox, Antrim, UK). High-sensitivity C-reactive protein (Hs-CPR), apolipoprotein A (Apo A), apolipoprotein B (Apo B), lipoprotein (a) (Lp (a)) and cystatin C were measured from the samples by immunoturbometric COBAS. Homocysteine was measured from samples by AXSYM ABBOTT. Serum adiponectin levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Biosource-Invitrogen Corporation, Carlsbad, CA). Serum H-FABP levels were determined using immunoturbidimetric method by automate (Randox, Antrim, UK).

Statistical Analysis: Database management and statistical analyses were carried out using SPSS (Statistical Package for the Sociological Sciences), version 18.0. Results are presented as means ± SD, or percentages. Means were compared using Student test. The relations between variables were assessed with Pearson's correlation analysis. The significance threshold was set at 5% ($p<0.05$).

RESULTS: Table1 shows the clinical profile between the patients with and without MetS. Of the 402 subjects, 209 were diagnosed as having MetS (57 male and 152 female). These patients had significantly higher levels of waist circumference, BMI, hypertension, fasting glucose, HbA1c, HOMA-IR, fasting insulin, triglycerides, total cholesterol, LDL-C, Apo B, Lp (a), urea, uric acid, cystatin C, GGT, ASAT, ALAT**,** homocycteine, hs-CRP, FFA and H-FABP, but significantly lower concentrations of adiponectin, HDL-C and Apo A1, as compared with those without MetS. No significant difference was observed in creatinine between the 2 groups.

TABLE 1: DEMOGRAPHIC CHARACTERISTICS AND BIOCHEMICAL DATA OF MetS GROUP AND CONTROL GROUP.

Parameters	Control group (n= 193)	MetS group (n= 209)	P value
Age (years)	50.3±10.6	58.9±10.7	0.026
Waist circumference (cm)	93.79±11.77	102.57±10.24	0.05
BMI (Kg/m^2)	26.93±4.68	30.85±5.01	0.014
Smoking (%)	8.1	0	$<10^{-3}$
Hypertension (%)	0	77	0.003
Fasting glucose (mmol/l)	5.18±0.65	8.52±3.94	$<10^{-3}$
HbA1C (%)	6.29±0.97	7.94±2.25	0.047
Fasting insulin (uU/ml)	8.26±2.67	13.61±5.74	0.002
HOMA-IR	1.90±0.67	5.22±3.72	$<10^{-3}$
Total cholesterol (mmol/l)	4.70±1.07	5.43±1.61	$<10^{-3}$
HDL-C (mmol/l)	1.36±0.35	1.16±0.36	$<10^{-3}$
LDL-C (mmol/l)	2.87±0.89	3.50±1.35	$<10^{-3}$
Triglycerides (mmol/l)	1.008±0.37	1.68±0.92	10^{-3}
Apo A1 (g/l)	1.69±0.29	1.30±0.37	$<10^{-3}$
Apo B (g/l)	0.90±0.23	1.09±0.26	$<10^{-3}$
Lp (a) (g/l)	0.21±0.14	0.39±0.34	$<10^{-3}$
Urea (mmol/l)	4.94±1.83	5.83±2.52	$<10^{-3}$
Creatinine (µmol/l)	69.60±23.86	74.63±42.12	NS
Uric acid (µmol/l)	201.63±69.71	235±95.23	$<10^{-3}$
Cystatin C (mg/l)	0.77±0.16	1.13±0.38	0.006
GGT (IU/L)	16.50±5.70	18.97±9.20	0.01
ASAT (IU/L)	19.56 ±7.009	20.99±7.83	0,054
ALAT (IU/L)	17.92±7.83	20.15±9.44	0.01
Adiponectin (mg/l)	19.93±7.95	12.21±7.58	0.042
Homocycteine (µmol/l)	9.92±3.49	13.70±5.76	$<10^{-3}$
Hs-CRP (mg/l)	1.97±1,17	5.34±5,61	$<10^{-3}$
FFA (µmol/l)	0.34±0.15	0.92±0.24	$<10^{-3}$
H-FABP (ng/ml)	3.78±1.04	9.80±4.75	$<10^{-3}$

Abbreviations: glycosylated hemoglobin (HbA1c), Homeostasis Model Assessment – Insulin Resistance (HOMA-IR), High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (apoA1), apolipoprotein B (apoB), lipoprotein (a) (Lp (a)), aspartate aminotransferase (AST), alanine aminotransferase (ALT), ɤ-glutamyltransferase (ɤGT) highsensitivity C-reactive protein (hs-CRP), free fatty acids (FFA), heart fatty acid binding protein (H-FABP).

The demographic and biochemical features in diabetic MetS patients and non-diabetic MetS patients are shown in **Table 2**. In this group of patients 51.67% were diabetic and 48.38% were non-diabetic. Statistical data processing revealed significantly higher fasting glucose, HbA1C, HOMA-IR, Lp (a), cystatin C, homocycteine, hs-CRP, FFA and H-FABP values but significantly lower concentrations of adiponectin and Apo A1 among diabetic MetS patients compared to the non-diabetic MetS patients.

TABLE 2: DEMOGRAPHIC CHARACTERISTICS AND BIOCHEMICAL DATA OF NON-DIABETIC MetS AND DIABETIC MetS.

Parameters	Non-diabetic MetS group (n= 101)	Diabetic MetS group (n= 108)	P value
Age (years)	58.35±11.76	59.46±9.83	NS
Waist circumference (cm)	101.42±9.76	103.02±9.72	NS
BMI (Kg/m^2)	30.75±4.68	30.95±5.35	NS
Smoking (%)	7.92	8.33	NS
Hypertension (%)	75	79	NS
Fasting glucose (mmol/l)	5.80±0.81	11.07±4.01	$<10^{-3}$
HbA1C (%)	6.69±1.35	9.11±2.30	$<10^{-3}$
Fasting insulin (uU/ml)	12.93±5.78	13.06±5.72	NS
HOMA-IR	3.51±1.55	6.82±4.40	$<10^{-3}$
Total cholesterol (mmol/l)	5.36±1.34	5.50±1.83	NS
HDL-C (mmol/l)	1.17±0.38	1.15±0.34	NS
LDL-C (mmol/l)	3.44±1.09	3.56±1.55	NS
Triglycerides (mmol/l)	1.68±0.99	1.68±0.85	NS
Apo A1 (g/l)	1.47±0.34	1.29±0.35	0.05
Apo B (g/l)	1.11±0.27	1.07±0.25	NS
Lp (a) (g/l)	0.34±0.26	0.43±0.40	0.07
Urea (mmol/l)	5.70±2.60	5.96±2.45	NS
Creatinine (µmol/l)	73.55 ±27.71	75.63±52.25	NS
Uric acid (µmol/l)	252.69±102.32	219.79±85.53	NS
Cystatin C (mg/l)	0.79±0.42	1.19±0.34	0.05
GGT (IU/L)	18.81±8.53	19.12±9.82	NS
ASAT (IU/L)	21.91±7.21	20.13±8.30	NS
ALAT (IU/L)	19.23±7.58	20.96±10.87	NS
Adiponectin (mg/l)	12.96±7.97	11.51±7.16	0.046
Homocycteine (µmol/l)	12.01±7.62	15.84±4.82	0.057
Hs-CRP (mg/l)	2.86±1,17	5.85±4,90	0.03
FFA(µmol/l)	0.44±0.23	0.96±0.24	$<10^{-3}$
H-FABP (ng/ml)	6.77 ± 1.80	12.63±4.92	$<10^{-3}$

Abbreviations: glycosylated hemoglobin (HbA1c), Homeostasis Model Assessment – Insulin Resistance (HOMA-IR), High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (apoA1), apolipoprotein B (apoB), lipoprotein (a) (Lp (a)), aspartate aminotransferase (AST), alanine aminotransferase (ALT), ɤ-glutamyltransferase (ɤGT) highsensitivity C-reactive protein (hs-CRP), free fatty acids (FFA), heart fatty acid binding protein (H-FABP).

Serum H-FABP levels were significantly elevated in MetS patients when compared with control subjects, respectively, (9.80±4.75 ng/ml, 3.78±1.04 ng/ml, $p<10^{-3}$). Serum levels of H-FABP were higher in patients with diabetic MetS than in patients without diabetic MetS, respectively, (12.63±4.92ng/ml, 6.77±1.80ng/ml, $p<10^{-3}$). There were statistically significant differences between patients without diabetic MetS and control subjects, 6.77±1.80 and 3.78±1.04 ng/ml, respectively, ($P<10^{-3}$). (**Fig.1**)

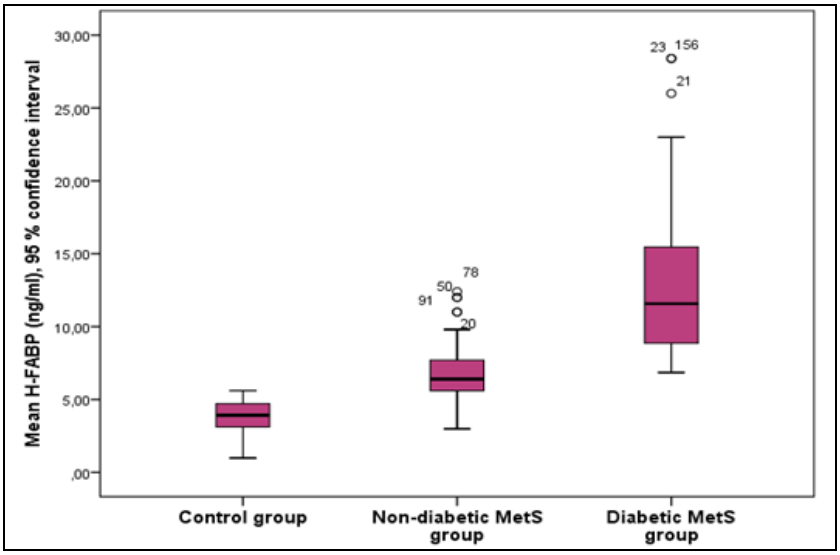

FIG. 1: SERUM H-FABP LEVELS IN PATIENTS WITH DIABETIC, NON-DIABETIC MetS AND CONTROL SUBJECTS.

Levels of H-FABP and FFA, after adjustment for age, gender, and BMI, were positively correlated with TG, FBS, hs-CRP and HOMA-IR, but inversely correlated with HDL-C and its main component apoA1. No significant correlations were identified between H-FABP and the other of MetS parameters. Serum adiponectin concentrations, after adjustment for above parameters, were positively correlated with HDL-C and ApoA1 but inversely correlated with TG, FBS, hs-CRP and HOMA-IR (**Table3**).

TABLE 3: CORRELATION OF SERUM H-FABP, ADIPONECTIN AND FFA CONCENTRATIONS WITH CARDIO-METABOLIC PARAMETERS AND INSULIN RESISTANCE MEASURED USING THE HOMEOSTASIS MODEL ASSESSMENT OF INSULIN RESISTANCE (HOMA-IR).

	TG	HDL-C	ApoA1	FBS	hs-CRP	HOMA-IR
H-FABP	0.341[a]	-0.153[a]	-0.294[a]	0.914[a]	0.236[a]	0.727[a]
FFA	0.178[a]	-0.168[a]	-0.126[a]	0.115[a]	0.135[a]	0.166[a]
Adiponectin	-0.167[a]	0.127[a]	0.092[a]	-0.119[a]	-0.109[b]	-0.154[a]

TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; apoA1: apolipoprotein A1; FBS: fasting glucose; hs-CRP: highsensitivity C-reactive protein; HOMA-IR: Homeostasis Model Assessment – Insulin Resistance; FFA: free fatty acids; H-FABP: heart fatty acid binding protein.

[a] $p<0.01$

[b] $p<0.05$

DISCUSSION: MetS is a defined cluster of cardiometabolic abnormalities that increases an individual's risk of T2D, CHD, and CVD. The chance of a person with MetS having a major CVD such as MI, stroke, or death was higher [22, 23]. MetS has also been shown to be related to an increased risk of subclinical ischemic heart disease[24]. Most of this excess risk is associated with an augmented prevalence of well-known risk factors such as hypertension, dyslipidemia and obesity in these patients [23, 25].

From this study we have found that the prevalence of MetS in the studied population was 52% based on NCEP-ATPIII criteria. Of the 209 MetS patients 51.67% was diabetics and represent higher levels of MetS components such as hyperglycemia, dyslipidemia and insulin resistance compared to non-diabetic MetS patients.

People with T2D have a higher cardiovascular morbidity and mortality, and are disproportionately affected by CVD compared with non-diabetic subjects [26]. Diabetic vascular disease is responsible for two-four-fold rise in the occurrence of CAD and stroke, and two-eight-fold improve in the risk of heart failure [27]. It has been estimated that about 47 million U.S. residents have MetS (including those with diabetes), corresponding to 22% of men and 24% of women [28], it has been demonstrated that individuals with this condition are at a three-fold greater risk of CHD and stroke, and more than a five-fold greater risk of cardiovascular mortality [29].

H-FABP is more specific for heart muscle than are other types of fatty acid binding protein [30, 31]. H-FABP is undetectable in normal conditions but is released rapidly from cardiomyocytes into circulating blood after myocardial damage. Previous studies have demonstrated that H-FABP is closely associated with acute coronary syndrome [32], hypertrophic and dilated cardiomyopathy, heart failure, stroke, obstructive sleep apnea syndrome and pulmonary embolism [14-21]. MI is one of the most serious challenges of contemporary cardiology. Among biochemical markers, H-FABP has a high potential as a marker for the early diagnosis of acute MI [33].

Further studies are required to investigate the relationship between H-FABP levels and long-term development of cardiac injury and atherosclerosis in patients with pre-diabetes [34]. This makes the estimation of H-FABP a suitable indicator for the early detection and quantification of myocardial tissue injury. Interesting results were obtained for the studied biochemical necrosis biomarkers regarding sensitivity, specificity, positive and negative predictive value and accuracy. H-FABP measured on admission showed as high as 94.7% sensitivity, 100% specificity, 100% positive predictive value, 93.4% negative predictive value and 97% accuracy [33]. H-FABP is a sensitive marker for the detection of cardiovascular damage, but is not 100% cardiac-specific, because of its presence in tissues outside the heart. In renal failure and skeletal muscle disease, it has limited diagnostic value [35].

Akbal et al [36, 37]. Demonstrated, and for the first time, that elevated circulating serum levels of H-FABP may provide important prognostic information in patients with MetS and reported that patients with MetS have increased serum levels of H-FABP, indicating its promise as a marker for detection of cardiac injury in patients with MetS. In healthy humans the normal range of H-FABP in serum or plasma has been reported to vary between 0.0 and 5.5 ng/ml [38, 39]. In our study, serum H-FABP levels were significantly elevated in MetS patients when compared with control subjects (9.80±4.75 ng/ml, 3.78±1.04 ng/ml, respectively, $p<10^{-3}$).

Alexander et al [40] have reported that MetS with diabetes is associated with the highest prevalence of coronary heart disease compared with MetS without diabetes in ≥50 years of age. In our study, serum H-FABP levels were significantly elevated in patients with diabetic MetS when compared in patients without diabetic MetS (12.63±4.92 ng/ml, 6.77±1.80 ng/ml, respectively, $p<10^{-3}$). These data suggest that an elevated level of H-FABP can identify that patients with diabetic MetS have an increased risk of atherosclerotic cardiovascular events, and patients with diabetic MetS may necessitate more hostile therapy.

Furthermore, our results showed that cardio metabolic parameters including HOMA-IR, TG, HDL-C, ApoA1, hs-CRP and FBS were significantly correlated with H-FABP. This suggests that the components of MetS and T2D can affect serum H-FABP levels. Those parameters were also significantly correlated with FFA and adiponectin, knowing as a potential biomarkers of vascular disease [38, 41].

CONCLUSION: Patients with MetS have an increased risk of death from cardiovascular diseases. H-FABP may provide important prognostic information in patients with MetS. Furthermore, H-FABP can be a step towards clinical tests that measure epigenetic alterations that can predict patients' risks of developing insulin, lipids and blood pressure phenotypes of MetS [37].

In conclusion, H-FABP seems to be a marker that will enable the detection of cardiac injury in the early asymptomatic period in patients with MetS. Further studies are required to investigate the relation between the value of H-FABP and the development of cardiac dysfunction in patients with MetS in the long term period.

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CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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