



Comparison between Fibroscan and Serum Taurine for Early Diagnosis of Liver Fibrosis in Egyptian Patients Infected with HCV

Ibrahim El Agouza¹, Rabab Fouad², Ramadan Ahmed³, Mohammed El-Sayed² and Amany Menshawy^{1*}

¹Faculty of Science, Zoology Department, Cairo University, Egypt

²Endemic Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt

³Hepatology Department, Ahmed Maher Teaching Hospital, Cairo, Egypt

*Corresponding author: Amany Menshawy, Faculty of Science, Zoology Department, Cairo University, Egypt, Tel: 01120070523; E-mail: Amany.Menshawy@gmail.com

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Abstract

Aim: The aim is to evaluate the role of measuring serum taurine level as an early biomarker for detection and staging of hepatic fibrosis in comparison to Fibroscan.

Patients and methods: 70 patients who are positive HCV are classified into five groups according to the scoring of Fibroscan. 10 healthy subjects were also enrolled as control group. Full clinical examination and complete biochemical analysis in addition to fibroscan and serum taurine as new marker are performed for all the selected patients and volunteers.

Results: Results showed non-significant changes in the most Analytical data between the five groups of patients and control group, but a significant Increment in the serum level of ALT and AST in F4 Stage is noticed and marked decrease in platelets also found in F4. The most interesting point recorded is that Serum taurine levels were exhibited a value markedly lower than that recorded in control group and its decline was related to the severity of the diseases.

Conclusion: It is suggested that the assessment of taurine level in sera of all hepatic patients beside fibroscan are of great value in the early diagnosis of any fibrotic changes in liver.

Keywords: Hepatic elastography; Hepatitis C virus; Liver biopsy; Liver fibrosis; Serum taurine level

Introduction

Hepatitis C virus (HCV) in Egypt has the largest epidemic of the world with a percentage of 15-20%, which is ten times greater than any other country [1-6]. The prevalence of HCV is highest in children and young adults who received parenteral anti-schistosomiasis treatment in the 1960s-1980s [7]. Egypt has the highest number of patients with genotype 4 HCV more than 90% of infected patients [8]. The vast majority of those infected Patients with HCV have not received treatment [9]. Currently Egypt has the greatest burden of advanced liver disease from HCV worldwide, the estimates suggest that in Egypt in 2013, there were 770,000 persons with cirrhosis, 16,000 HCV-related HCC cases and 33,000 HCV-related to liver deaths [10]. Patients with hepatitis B and hepatitis C virus infections are at high risk for development of hepatic fibrosis that may eventually develop cirrhosis and hepatocellular carcinoma [11]. Liver fibrosis in chronic liver disease, is characterized by excessive accumulation of an extracellular matrix, in response to chronic inflammation. Chronic hepatitis C infection represents the most common cause of hepatic fibrosis in Egypt [12].

Liver biopsy remains an important tool in the evaluation and management of liver disease, but it has several limitations invasive test

such as pain and bleeding. The sample resulting from liver biopsy is only a very small piece of the liver, which can lead to incorrect staging if this sample is not representative of the rest of the liver. Besides, different pathologists can interpret the same sample differently, which can result in discrepancies in liver disease staging [13].

To overcome these limitations, a new method for the staging of liver fibrosis is required. This technique must be non-invasive, fast, safe and reliable [14]. Transient elastography (TE) using Fibroscan is a relatively recent non-invasive method useful for staging of hepatic fibrosis [15]. TE was considered successful only if at least ten valid Measurements were performed on each patient. The success rate at least 60%, and an interquartile range of <30% of the value of the median performance of TE can be limited in obese patients also is impossible in patients with ascites. As TE waves cannot penetrate into ascites, older age and feature of the metabolic syndrome [16].

Taurine, 2-amino-ethanesulphonic acids, (Tau) an essential amino acid, present at high concentrations in the liver [17]. It has various physiological functions and protective properties including protection against various types of hepatic damage [18]. Tau has also been shown to have hepatoprotective effects that are often accompanied by reduced endoplasmic reticulum (ER) stress, oxidative stress, production of inflammatory, fibrogenic mediators and activation of stellate cells [18,19].

Mice with hetero and homozygous knockout of the Tau transporter show chronic liver disease characterized by fibrosis, inflammation, and hepatocyte apoptosis [20]. Tau possesses anti-inflammatory and immune-regulatory properties [21]. In iron-potentiated alcoholic liver fibrotic rats, Tau restored mitochondrial function, prevented DNA damage and apoptosis. It reduced reactive oxygen species formation, curtailed the production of inflammatory and fibrogenic mediators and the activation of stellate cells [19,22]. More over, it was suggested that assessment of taurine level in sera of patients with high risk for cancer breast or uterus are of great value in the early diagnosis of malignant changes in both organs [23,24]. and more recently it was advice to use serum taurine level in diabetic patients as a pre-early marker for diabetic retinopathy [25]. Also, it can induce apoptosis and inhibit the proliferation of HCC HepG2 cells [26] and induced apoptosis of human colon cancer [27]. Tau also could prevent the development of ameliorates glycemia, the action of insulin, and dyslipidemia in type 2 diabetes mellitus (T2DM) [28]. Another study showed that post-treatment supplementation of taurine is recommended for T2DM [29].

Several studies have demonstrated that exogenous supplementation with Tau can prevent liver injury caused by different harmful substances as well as inhibit extracellular matrix (ECM) molecules deposition on the damaged liver and stop the process of liver fibrosis, protect hepatic tissue and hepatocytes against various substrates, inducing hepato toxicities, oxidative stress, and hepato carcinogenesis [18,20,30,31]. Recently, taurine was used to ameliorate hepatotoxic effect of dinitrotoluene in rats [32].

Patients and Methods

All the patients first received information on the study from their referring physician and were asked to sign an informed consent form. This study included 70 patients aged between 29-65 years (males and females), were selected from our patient's clinics at the Hepatology department, Ahmed Maher Teaching Hospital, Cairo, Egypt.

Those patients presented with abdominal troubles and signs of liver impairment, and we rejected all patients presented with kidney impairment or diabetes. They were classified into 5 groups according to the scoring of Fibroscan. 10 healthy subjects were also enrolled as control group.

TE qualities were further changed over in the comparing semi quantitative fibrosis score of METAVIR. It is based on a semi quantitative 5-point scale from 0 to 4: F0, the absence of parenchymal fibrosis; F1 enlarged fibrotic portal tract; F2, periportal or initial portal-portal septa but intact architecture; F3, architectural distortion but no obvious cirrhosis; and F4, cirrhosis. The conversion of TE values into the corresponding METAVIR stage was made by means of validated cutoff values (i.e., F0-F1=2.4-7 kPa, F2=7.1-9.5 kPa, F3=9.6-12.5 kPa and F4 N 12.5 kPa) The change of TE values into the relating METAVIR stage was made by means of validated cutoff values [33,34]. The patients and volunteers were classified as follows:

- Control group (No=10 healthy subjects)

- Stage 0 group (No=10 patients)
- Stage 1 group (No=12 patients)
- Stage 2 group (No=13 patients)
- Stage 3 group (No=15 patients)
- Stage 4 group (No=20 patients)

Full clinical examination, complete biochemical analysis (including liver and complete blood picture and TSH). Virus detection done by the polymerase chain reaction (PCR), Fibroscan was measured for all patients and control after 12 hours fasting. For the whole selected subjected, after 12 hours fasting, 10 ml of venous blood was collected, in plain tube and allowed to clot for 1/2 an hour, after which it was centrifuged at 3,000 rpm for 10 min. The serum was separated and stored at -20°C to avoid loss of biological activity until the batch analysis for serum taurine. It was mesasured by high performance liquid chromatography (HPLC) according to pre-Colum extraction and derivatization methodology [35].

TE was done with FibroScan (Echosens, Paris, France) using a normal probe (no XL probe was used), this measurement is taken on the right lobe of the liver, through intercostals spaces with the patient lying in dorsal decubitus with the right arm in maximal abduction. The tip of the transducer probe is covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface. This volume is at least 100 times bigger than a biopsy sample, and is therefore far more representative of the hepatic Parenchyma, a cut-off of <5.5 kPa was considered to indicate normal [15].

Statistical Analysis

After confirmation of normal distribution for all variables, the significance of differences was evaluated by paired t-test or analysis of variance (ANOVA). Relationships between variables were analyzed by simple correlation analysis. Data are expressed as mean SD, and a value of P<0.05 was the criterion for statistical significance.

Results

Our study includes 70 patients (36 male and 34 female) Those patients were classified into five groups according the degree of fibrosis including (F0, F1, F2, F3, F4), beside 10 healthy subject's Negative PCR for HCV were enrolled as control group.

Only those patients who had reliable Fibroscan were taken for analysis. A total of 76 patients were enrolled in the study. Of 76 patients, six had unreliable Fibroscan so a total of 70 patients were included in analysis.

For the hematological parameters the results showed non-significant changes (P>0.05) in haemoglobin (Hb), Red blood cells (RBCs), White blood cells (WBCs) and platelets in all groups as shown in Table 1. Only significant change in the platelets count was recorded between f3 and f1 (P<0.00), and also between f4 and f1 (P<0.000).

Group	Hb g/dl	RBCs 10 ⁶ /cmm	WBCs 10 ³ /cmm	Platelets 10 ³ /cmm
Control (n=10)	13.30 ± 1.00	4.33 ± 0.27	6.00 ± 1.12	243.70 ± 31.59
F0 (n=10)	12.52 ± 1.56 NS	4.23 ± 0.52 NS	6.48 ± 1.98 NS	218.60 ± 40.04 NS

F1 (n=12)	12.88 ± 1.34 NS	4.38 ± 0.41 NS	5.73 ± 1.81 NS	240.67 ± 58.15 NS
F2 (n=13)	12.70 ± 1.79 NS	4.25 ± 0.56 NS	6.68 ± 1.41 NS	224.38 ± 82.07 NS
F3 (n=15)	13.45 ± 1.42 NS	4.47 ± 0.45 NS	4.87 ± 1.35 d*	174.20 ± 43.49 a, c**, d*
F4 (n=20)	13.36 ± 1.03 NS	4.40 ± 0.39 NS	4.64 ± 1.21 a, b, c, d*, e ns	157.80 ± 45.26 a, c***, b, d**, e ns

Table 1: Blood picture in different groups of patients. Data are expressed as mean ± SD. a: refers to control group, b: refers to stage 0 group, c: refers to stage 1 group, d: refers to stage 2 group, e: refers to stage 3 group. p value > 0.05 Non-significant (ns), *Significant at level < 0.01, **highly Significant at level < 0.001, ***very highly Significant < 0.000 p value 0.01 to 0.05 Significant*, p value 0.001 to 0.01 High significant**, p value 0.0001 to 0.001 Extremely significant***.

Moreover Table 2 showed non-significant changes (P > 0.05) in the different fibrotic groups and control. A significant Increment in the serum level of ALT and AST in F4 Stage is noticed. (Alanine transaminase (ALT), Aspartate transaminase (AST), total bilirubin, Albumin, the international normalized ratio (INR) between

Group	ALT U/L (0-50)	AST U/L (0-40)	Total bilirubin mg/dl (0-1)	Albumin g/dl (3.5-5.5)	INR (1-1.3)
Control (n=10)	25.00 ± 2.98	22.40 ± 3.44	0.81 ± 0.11	4.37 ± 0.18	1.01 ± 0.14
F0 (n=10)	41.20 ± 18.43 NS	47.50 ± 19.46 NS	0.67 ± 0.25 NS	3.87 ± 0.20 NS	1.03 ± 0.85 NS
F1 (n=12)	41.08 ± 11.65 NS	48.50 ± 18.92 NS	0.93 ± 0.21 NS	3.94 ± 0.31 NS	1.08 ± 0.08 NS
F2 (n=13)	45.31 ± 20.06 NS	52.54 ± 21.06 a**	1.00 ± 1.01 NS	4.08 ± 0.48 NS	1.08 ± 0.18 NS
F3 (n=15)	52.33 ± 31.04 a*	54.20 ± 25.33 a**	1.03 ± 0.51 NS	3.97 ± 0.53 a*	1.11 ± 0.19 NS
F4 (n=20)	61.30 ± 47.43 a***	67.80 ± 38.08 a***	0.87 ± 0.24 NS	3.68 ± 0.33 a***, d, e**, c*	1.07 ± 0.32 NS

Table 2: Liver functions and INR in different groups of patients. Data are expressed as mean ± SD. a: refers to control group, b: refers to stage 0 group, c: refers to stage 1 group, d: refers to stage 2 group, e: refers to stage 3 group, p value > 0.05 Non-significant(ns), *Significant at level < 0.01, **highly Significant at level < 0.001, ***very highly Significant < 0.000, p value 0.01 to 0.05 Significant*, p value 0.001 to 0.01 High significant **, p value 0.0001 to 0.001 Extremely significant***

There was a significant difference in median LSM value in patients with F0 (4.70 ± 0.58) in comparison to patients having mild fibrosis (F1 6.29 ± 0.61, F2 8.11 ± 0.74) and advanced fibrosis (F3, F4) (10.92 ± 0.96 vs. 24.18 ± 15.44). The difference between median LSM value of mild and advanced fibrosis was also statistically significant.

Group	TSH uIU/MI 0.30 5.00	PCR IU/mL Less than 16	Fibroscan kPa 0-75	Taurine µmol/L Up to 55
Control (n=10)	1.05 ± 0.70	Less than 16	00 ± 00	62.50 ± 3.37
F0 (n=10)	1.69 ± 1.66 NS	569693.3 ± 326391.1 a***	4.70 ± 0.58 a***	40.63 ± 3.88 a***
F1 (n=12)	1.53 ± 1.03 NS	692273.6 ± 769579.5 a***	6.29 ± 0.61 a, b ns	33.52 ± 2.35 a, b***
F2 (n=13)	1.61 ± 0.97 NS	699066.5 ± 1322773 a***	8.11 ± 0.74 a*, b, c ns	28.17 ± 4.08 a, b***, c*
F3 (n=15)	1.72 ± 1.44 NS	1467885 ± 1957105 a***	10.92 ± 0.96 a**, b, c, d ns	24.44 ± 1.56 a, b, c***, d*
F4 (n=20)	2.31 ± 0.97 NS	3124404 ± 8163084 a, b, c, d, e***	24.18 ± 15.44 a, b, c, d, e***	20.64 ± 2.77 a, b, c, d***, e**

Table 3: TSH, PCR, Fibroscan, Taurine in different groups of patients. Data are expressed as mean ± SD. a: refers to control group, b: refers to stage 0 group, c: refers to stage 1 group, d: refers to stage 2 group, e: refers to stage 3 group, p value > 0.05 Non-significant (ns), *Significant at level

<0.01, **highly Significant at level <0.00, ***very highly Significant <0.000, p value 0.01 to 0.05 Significant *, p value 0.001 to 0.01 High significant **, p value 0.0001 to 0.001 Extremely significant****.

The most interesting point in this work was illustrated in Table 3, when the serum level of taurine recorded in F0 was highly significantly decreased (40.63 ± 3.88) regarding to its level recorded in control group (62.50 ± 3.37). This level was decreased parallel to the degree of fibrosis from F1 (33.52 ± 2.35) To F2 (28.17 ± 4.08) To F3 (24.44 ± 1.56) Up to F4 (20.64 ± 2.77).

Discussion

Chronic hepatitis C remains a worldwide problem with highly prevalence rates in developing countries. Egypt, for example, the prevalence approaches 20% of a 90 million population [1-6]. Also has the highest number of Patients with genotype 4 HCV more than 90% of infected patients [8]. Till now Liver biopsy is considered the gold standard technique for the evaluation of liver fibrosis. But there are many drawbacks of liver fibrosis like invasive test, pain and bleeding [13]. To avoid this limitation, we measured liver stiffness by TE using fibroscan device to assess the different degree of liver fibrosis (F0, F1, F2, F3, F4). This device is non-invasive, safe and reliable [14]. But it is value is limited in obese patients also is impossible in patients with ascites. As TE waves cannot penetrate into ascites, older age and feature of the metabolic syndrome [16].

Our result showed no significant change in Liver enzymes. Confirming our result there are reports of marked fibrosis (5%-30%) and even cirrhosis (1.3%) in persons with normal ALT value [36,37]. While taurine levels were exhibited a value markedly lower than control group according to the severity of the diseases that consider as early diagnosis and more accurate than other routine test like AST, ALT, Platelets. There is a study exploring the relationship between plasma amino acid profiles and liver fibrosis, it is clearly demonstrated that abnormal sulfur containing amino acids (SAA) patterns in patients with chronic hepatitis C are correlated with the progression of liver fibrosis [38]. Tau as an antioxidant can increase hepatic self-antioxidant capacities and decreased lipid peroxidation in high-fat/cholesterol dietary hamsters. Taurine supplementation can reduce serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) [39].

Taurine not only can act as a direct antioxidant by scavenging free radicals and inhibiting lipid peroxidation (LPO), it also can stimulate the activity cytoprotective enzymes when the cell is exposed to stressful conditions [40]. The hepatic cell membrane can automatically repair after alcohol withdrawal if the damage is not serious, while taurine accelerates the repair of hepatic cells, decreasing membrane permeability and inhibiting the release of ALT and AST and improve the serum levels bilirubin [29,41]. Moreover, taurine supplementation also could downregulate these granulomatous and fibrogenic mediators in the liver of *S. japonicum*-infected mice which further confirmed the anti-granulomatous and anti-fibrotic effects of taurine during *S. japonicum* infection [42]. In acute liver disease model in a rat induced by a single administration of CCl_4 , showed that taurine treatment prevented hepatocellular necrosis, lipid peroxidation, mitochondrial abnormalities. Moreover, taurine also inhibits the transformation of HSCs induced by CCl_4 observed by electron microscopy [29]. Taurine significantly decreased hepatic fibrosis and fibrogenesis of isolated hepatic stellate cells, which are converted to myofibroblasts by oxidative stress in cirrhotic liver, through inhibition

of transforming growth factor- β expression. In CCl_4 -administered rats, the taurine concentration in the liver, plasma, and other tissues was significantly decreased [43].

Taurine may be used in combination with Silymarine as an additional adjuvant therapy to cure liver diseases induced by CCl_4 such as cirrhosis and viral hepatitis [44].

Regarding fibroscan, our result showed that the median stiffness values increased as the fibrosis stage increase. but there some factors associated with reading unreliability were $\text{BMI} > 30 \text{ kg/m}^2$ in our study we could not do TE in four patients due to obesity their BMI is greater than 32 kg/m^2 . It postulated that in population as in our country high proportion of patients have $\text{BMI} > 30 \text{ kg/m}^2$, elastometry should be difficult to use because it could overestimate liver fibrosis in a high proportion of patients [45]. Also, TE Failure in two patients as no valid shot after at least ten attempts.

The most attracted point is when fibroscan diagnosis patients at f0 usually regular check-up is the only advice from doctor to all patients have stage zero of stiffness. But in contrast, the most impressive observation in our work is the result of antioxidant taurine which showed highly significant decrease in their serum levels in all patients staging zero (40.63 ± 3.88) when compared to normal control group (62.50 ± 3.37) which can be consider as an early sign of liver impairment and the immediate induction of its treatment. The classification of Fibroscan will be enhanced by Taurine level measurements. Within each Fibroscan class, the taurine can play an important to measure any slight deterioration that may happen in the patient's status. In case of dealing with patients classified as f0, the taurine level may represent another real evaluation of the possibility of patient's deterioration as shown in this study. It has been shown that the taurine level can detect any slight shift from the normal case which may anticipate any future liver problem. It was postulated that patients with stages F0-F1 are considered much less likely to progress and may be spared from treatment, and Patients with stage F2-F4 have a higher chance of development of cirrhosis within the following 5-10 years and are considered eligible for treatment [46]. In stage F4 the stiffness of fibroscan range between 12.6-64.0 that is very wide range. While taurine level in this stage is 20.64 ± 2.77 .

In our study patients with F4 stiffness of fibroscan between (12.6-64.0) as shown in Table 3, that high stiffness of patients may be highly susceptibility for cancer. TE value was selected as one of independent risk factors for HCC development, and patients with higher value had significantly higher risk of HCC development [47].

Previous research showed stage F4 Fibrosis is important differentiating mark, where patients with cirrhosis need closer monitoring, screening for varices and HCC is recommended, response to therapy is diminished, and these patients may not tolerate many drugs involved in the treatment of HCV [46]. There is no doubt that taurine is considered as powerful hepatoprotective substance that can protect the hepatocyte through different mechanisms [31,48,49].

Our result encourages us form new classification for cirrhotic patients depend on taurine level. Hepatic patients consider safety when taurine level above $50 \mu\text{mol/L}$, when taurine level exhibited value between (40-50) hepatic patients are highly susceptible for many

hepatic complication, advanced liver cirrhosis and susceptibility for HCC increased when taurine level decreased than 30 $\mu\text{mol/L}$.

A lot of paper consider 20 $\mu\text{mol/L}$ of taurine level as a cut of value of tumour by other means any patients exhibited less than 20 $\mu\text{mol/L}$ must be suffer from cancer in elsewhere of body [23,24,26,27]. Because they suggested that taurine is high sensitive nonspecific tumour marker.

So, taurine level may be represented an early alarm predictive tool in patients suffering from liver complications. Taurine level may play a complementary important role with the Fibroscan to monitor the patient's status and progress within each class of fibroscan. In other word, within each fibroscan class, many subclasses may be generated according to the taurine level. This may be measure whether the patients within a class is stable or is deteriorating. So, integrating both the Fibroscan and Taurine level measurement may result in a more accurate and direct monitoring of the patient status. It may represent a warning for the physician to take the suitable action.

In conclusion based on the results of the present investigation, we strongly suggested the assessment of serum taurine level in all hepatic patients especially +ve B, +ve C beside fibroscan and biochemical analysis especially in F4 because those patients are highly susceptible for HCC. So, we must not let patients reach to such a high score of fibrosis, we suggest giving them especial dose of taurine as hepatoprotective drug in F0 stage.

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