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COMPARISON BETWEEN SERUM TAURINE AND SPECIFIC TUMOR MARKERS FOR EARLY DETECTION AND DIAGNOSIS OF HCC IN EGYPTIAN PATIENTS

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ABSTRACT

Introduction: Taurine has been demonstrated to have a direct and indirect antioxidant effect and to display antineoplastic activity by preventing angiogenesis and enhancing tumor cell apoptosis. Also it was suggested that measurement of serum taurine level in hepatic patients beside fibroscan is of great value in the early diagnosis of any fibrotic and cancerous liver changes. **Objectives:** To correlate serum taurine level with the levels of the specific tumor markers (α- fetoprotein and α-L-fucosidase) for early diagnosis of different stages of HCC in Egyptian patients. **Methods:** This observational case-control study was conducted in the Tropical Medicine Department, Ahmed Maher Teaching Hospital. Eighty hepatic patients were assigned to three groups (Chronic hepatitis, Cirrhosis and HCC). Twenty healthy subjects were enrolled as a control group. Serum levels of AFP, AFU, and taurine beside complete biochemical analysis and liver biopsies from all selected patients were done. Patients who accepted to be a candidate for living donor liver transplant (LDLT) were referred to Ain Shams University Specialized Hospital (ASUSH) liver transplant unit. **Results:** A total of 80 patients were randomized into three groups (Chronic hepatitis (n = 20), Cirrhosis (n = 20) and HCC (n = 40)) and 20 volunteers as a control group. The serum levels of (AFP, AFU and Tau) showed significant differences among three patient groups (P=0). While AFP and AFU levels showed non-significant differences among HCC groups (grade 1,2 and 3), (P=0.057) and (P=0.584) respectively in contrast to Tau levels which were significantly different among HCC groups (P=0).Twenty-two patients who accepted to be a candidate for the LDLT were referred to Ain Shams University Specialized Hospital (ASUSH) liver transplant unit. **Conclusion:** Serum taurine level beside (AFP and AFU) are of great value in early diagnosis in HCC Egyptian patients and may have a rule in identifying end-stage liver disease (ESLD) patients candidate for LDLT.

KEYWORDS: Alpha-fetoprotein (AFP), Alpha-fucosidase (AFU), End-stage liver disease (ESLD), Hepatocellular carcinoma (HCC), living donor liver transplant (LDLT), Taurine (Tau).

INTRODUCTION

Egypt is considered one of the largest endemic area of hepatitis C in the world. Hepatocellular carcinoma (HCC) is a primary malignancy of the liver especially in patients with chronic liver disease and cirrhosis.[1] HCC is the fifth most common worldwide cause of cancer-related death.[2] In Egypt, HCC forms 11.75% of the malignancies of all digestive system and 1.68% of the total malignancies.[3]

With the progress in tumor biology, the rule of biomarkers for early diagnosis of tumor progression has attracted many of research interest to detect novel markers for cancer.[4][5]

Current gold standard tumor biomarkers for patients at risk for HCC, are alpha-fetoprotein (AFP) and alpha-L-fucosidase (AFU). AFP levels may be elevated in the early stages of HCC and thereafter drop before increasing again as the disease progress. AFP sensitivity

ranges between 40-65% and specificity within the 76%-96%.[6] AFU serum level was recorded to be elevated at least 6 months before ultrasonography detection in 85% of HCC patients.[1]

Taurine (2 aminoethane sulfonic acid) is widely distributed in mammalian cells. Tau is a conditionally essential amino acid produced in the liver from methionine and cysteine metabolism. It modulates a verity of cellular functions, neurotransmitter modulation and osmoregulation.[7] Moreover, it has a protective effect against hyperglycemia[8] and hypertension.[9]

It was suggested that Tau has a hepatoprotective effect,[10] as it may ameliorate hepatic fibrosis by inhibiting extracellular matrix deposition.[11] Several studies demonstrated that serum taurine level was used as a biomarker for early diagnosis of breast and uterine carcinoma.[12][13] Recently it was postulated that serum Tau level was used as a pre-early marker for diabetic complications in patients with diabetic foot and diabetic retinopathy.[14],[15] Moreover, Tau level was used for early diagnosis of liver fibrosis in HCV Egyptian patients.[16] Liver transplantation became the only definitive therapy for ESLD and HCC patients.[17] The aim of the study was to correlate serum taurine level with the levels of the specific tumour markers (α- fetoprotein and α-L-fucosidase) for early diagnosis of different stages of HCC in Egyptian patients.

MATERIALS AND METHODS

This observational case-control study involved three groups of total eighty patients aged between 20-70 years were selected from Tropical Medicine Department, Ahmed Maher Teaching Hospital and 20 volunteers as a control group. One hundred sixteen hepatic patients were assessed for eligibility but only 80 patients were included in the study after exclusion of 36 patients (19 patients due to inability to obtain a liver biopsy for diagnosis, 13 patients due to bleeding tendency and 4 patients with tense ascites). Full clinical examination, abdominal ultrasound, CT scan in addition to esophagoscopy were done for all patients. Serum levels of AST, ALT, total bilirubin, prothrombin concentration, fasting blood glucose, CBC (HB, RBCs, WBCs, and Platelets), urea and creatinine were also measured for all. In addition, serum levels analysis of specific liver tumors markers including AFP, AFU beside taurine as a possible new marker were done for all patients. Liver cells were examined histopathologically after taking a liver biopsy from selected patients (cirrhotic and HCC). All subjects gave written informed consent after the nature of the procedure was explained. They were classified into three groups according to final diagnosis beside twenty healthy subjects were also recruited as a control group.

1. Control group (NO=20). 2. Chronic hepatitis group (NO=20)

3. Cirrhosis group (NO=20) 4. HCC group (NO=40).

HCC group patients were subdivided into three groups according to the histopathological results (grade 1,2 and 3)

Patients were assessed by liver transplant team from (ASUSH) and patients accepted to be LDLT candidate were referred to (ASUSH) liver transplant unit to complete their workup.

Blood samples

The blood samples were drawn in the morning after 12 hours fasting. A portion of blood was collected on EDTA for determination of CBC. The other portion left to clot for 2 hr at 4C° without shaking, then centrifuged at 3000 rpm for 10 min. The serum was separated into two parts. The first was used to measure AST, ALT, T.billirubin, Albumin, urea, and creatinine. The second part was stored at -20C tell used for the assay of taurine. The blood in EDTA tubes was used within 2-3hr of a collection to perform complete blood count (CBC), white blood cells (WBCs), red blood cells (RBCs), hemoglobin (Hb) and platelets (PLT) using cell Dyne 1700 electronic counter (Sequoia-Turner corporation, California, USA).

Alanine Aminotransferase (ALT), this is an optimized standard UV method according to European Committee for Clinical Laboratory Standard (ECCLS), 1998.

Aspartate Aminotransferase (AST); this is an optimized standard UV method according to Scandinavian Committee on Enzyme (SCE), 1974.

Tumor markers

AFP: by using ELISA kits. The kit provides materials for the quantitative measurement, this kit was obtained from Nordic immunology.

AFU: it was determined calorimetrically. Cat.NO., (DZ082B-Con) - Diazyme.

Taurine: determined by High-Performance Liquid Chromatography according to the pre-column extraction and derivatization methodology of McMahon et al. in the present work we use the Shimadzu, Japan HPLC model LC-10 AT.

Statistical analysis

IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017-2018) was used for data analysis. Data were expressed as Mean±SD for quantitative parametric measures in addition to median and percentiles for quantitative non-parametric measures. Total sample size 80 cases (taurine level among patients groups was used as a primary outcome with proposed large effect size (0.8) and alfa =0.05 and power =0.80.

The following tests were done:

1. Comparison between two independent mean groups for parametric data using Student t-test.

2. Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test.
3. Comparison between more than 2 patient groups for parametric data using Analysis of Variance (ANOVA).
4. Comparison between more than 2 patient groups for non-parametric data using Kruskal Wallis test.
The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly sig.
5. Diagnostic validity test: It includes:
a. The diagnostic sensitivity: It is the percentage of diseased cases truly diagnosed (TP) among total diseased cases (TP+FN).
b. The diagnostic specificity: It is the percentage of non-diseased truly excluded by the test (TN) among total non-diseased cases (TN+FP).
c. The predictive value for a +ve test: It is the percentage of cases truly diagnosed among total positive cases.
d. The predictive value for a -ve test: It is the percentage of cases truly negative among total negative cases.
e. The efficacy or the diagnostic accuracy of the test: It is the percentage of cases truly diseased plus truly non-diseased among total cases.

RESULT

A total of 80 patients and 20 volunteers as a control group were divided into four groups: Control group (NO=20), Chronic hepatitis group (NO=20), Cirrhosis group (NO=20) and HCC group (NO=40) (grade 1 = 15 patients), (grade 2 = 12 patients), (grade 3 = 13 patients).

Comparing the parametric parameters between the control and hepatic patients **(Table 1**) results showed significant differences ($P < 0.01$) except for FBS ($P > 0.05$). Comparing the non-parametric parameters between control and hepatic patients **(Table 2)** results showed non-significant differences ($P > 0.05$) for WBC count, but notably, there were significant differences between control and hepatic patients regarding serum albumin, AFP and AFU ($P < 0.01$).

Using Analysis of Variance (ANOVA) to compare between three patients groups, data shown in **Table 3**. $P < 0.05$ was detected in all parametric parameters among patients group. While among HCC groups (1,2 &3), there was no significant difference except for prothrombin concentration (P=0.035) and taurine (P=0).

Using Kruskal Wallis test to compare non-parametric data between three patients groups, data shown in **Table 4**. AFP and AFU ($P = 0$) was detected among three patients groups, while AFP (P=0.057) and AFU (P=0.584) were noticed among HCC groups (1,2 &3).

Using diagnostic validity test **Table 5** The best cutoff value for Taurine at 19.6, below which the sensitivity or ability to discriminate HCC from non-HCC = 100% compared to 82.5% for AFP and 90.0% for AFU; the specificity or ability to discriminate non-HCC = 100% compared to 96.7% for AFP and 95.0% for AFU. The predictive value of the negative test = 100% compared to 89.2% for AFP and 93.4% for AFU. The predictive value of the positive test = 100% compared to 94.3% for AFP and 92.3% for AFU. The efficacy = 100% compared to 91.0% for AFP and 93.0% for AFU.

The best cutoff value for Taurine at 14.3, below which the sensitivity or ability to discriminate HCC grade 3 from HCC grade 1 and 2 = 92.3% compared to 61.5% for AFP and 53.8% for AFU; the specificity = 100% compared to 85.2% for AFP and 51.9% for AFU. The predictive value of the negative test = 96.4% compared to 82.1% for AFP and 70% for AFU. The predictive value of the positive test = 100% compared to 66.7% for AFP and 35% for AFU. The efficacy = 97.5% compared to 77.5% for AFP and 52.5% for AFU.

The best cutoff value for Taurine at 16.65, below which the sensitivity or ability to discriminate HCC grade 2 from HCC grade 1 = 92.3% compared to 92.3% for AFP; the specificity = 100% compared to 50 % for AFP. The predictive value of the negative test = 93% compared to 87.5% for AFP. The predictive value of the positive test = 100% compared to 63.2% for AFP. The efficacy = 96.3% compared to 70.4% for AFP. There was no detected best cutoff for AFU to discriminate between HCC grade 1 and 2.

Confirming all previous investigation, the histopathological examination of liver biopsies taken from the selected patients showed the typical picture for cirrhosis with massive regenerated modules surrounded by very vascular periportal areas rich in blood capillaries and lymphatic infiltration **Figure. 1**. Also, **Figure 2-4** showed a hepatocellular carcinoma with highly vascular stroma supporting the tumor cells.

Twenty-two patients accepted to be a candidate for LDLT were referred to (ASUSH) liver transplant unit to complete their laboratory and imaging workup. Eight patients were cirrhotic, fourteen patients were HCC stage1. Nine patients of which were admitted to the liver transplant specialized intensive care unit in ASUSH due to grade II hepatic encephalopathy in 5 patient, spontaneous bacterial peritonitis (SBP) in one patient and upper GIT bleeding in 3 patients. All patients transferred to the ICU were managed according to the protocol scheduled for hepatic patients prepared for LDLT and after being hemodynamically stable and fully conscious they were transferred to the liver transplant unit in ASUSH under the supervision of LDLT medical team.

Table 1: Control versus patients parametric parameters.

P	Mean	n	Group	
	33.2(7.302)	20	Control	Age Years
0.001	40.05(4.718)	20	Hepatitis	
	4.41(0.4051)	20	Control	RBCs (x 10^6/dl)
0.005	4.045 (0.3706)	20	Hepatitis	
	13.545(1.2816)	20	Control	Hb gm/dl
0.001	12.3(0.8663)	20	Hepatitis	
	86.75(6.576)	20	Control	FBS mg/dl
0.054	82.1(8.097)	20	Hepatitis	
	21.85(3.468)	20	Control	AST U/L
0	78.6(21.967)	20	Hepatitis	
	23.5(3.532)	20	Control	ALT U/L
0	105.55(29.726)	20	Hepatitis	
	98.75(1.293)	20	Control	Prothrombin concentration %
0	92.95(4.548)	20	Hepatitis	
	63.15(3.77352)	20	Control	Taurine µmol/L
0	46.74(3.31224)	20	Hepatitis	
	33.2(7.302)	20	Control	Age Years
0	45.4(5.853)	20	Cirrhosis	
	4.41(0.4051)	20	Control	RBCs (x 10^6/dl)
0	3.495(0.4989)	20	Cirrhosis	
	13.545(1.2816)	20	Control	Hb gm/dl
0	10.53(1.6226)	20	Cirrhosis	
	86.75(6.576)	20	Control	FBS mg/dl
0.908	86.4(11.659)	20	Cirrhosis	
	21.85(3.468)	20	Control	AST U/L
0	42(10.433)	20	Cirrhosis	
	23.5(3.532)	20	Control	ALT U/L
0	46.15(13.068)	20	Cirrhosis	
	98.75(1.293)	20	Control	Prothrombin concentration %
0	63.7(7.299)	20	Cirrhosis	
	63.15(3.77352)	20	Control	Taurine µmol/L
0	28.865(3.07661)	20	Cirrhosis	
	33.2(7.302)	20	Control	Age Years
0	53.4(7.225)	40	HCC	
	4.41(0.4051)	20	Control	RBCs(x 10^6/dl)
0	3.728(0.5179)	40	HCC	
	13.545(1.2816)	20	Control	Hb gm/dl
0	11.55(1.3832)	40	HCC	
	86.75(6.576)	20	Control	FBS mg/dl
0.115	90.33(10.598)	40	HCC	
	21.85(3.468)	20	Control	AST U/L
0	44.05(12.308)	40	HCC	
	23.5(3.532)	20	Control	ALT U/L
0	48.05(14.636)	40	HCC	
	98.75(1.293)	20	Control	Prothrombin concentration %
0	53.68(9.124)	40	HCC	
	63.15(3.77352)	20	Control	Taurine µmol/L
0	16.1473(2.3146)	40	HCC	

Data are expressed as mean ±SD

Table 2: Control versus patients non- parametric parameters.

P	median	n		
	5.6	20	Control	WBC (x 10^3/dl)
0.31	5.35	20	Hepatitis	
	243.5	20	Control	Platelets (x 10^3/dl)
0.064	210.5	20	Hepatitis	
	19.5	20	Control	Urea mg/dl
0.157	21.5	20	Hepatitis	
	0.7	20	Control	creatinine mg/dl
0.069	0.8	20	Hepatitis	
	4.5	20	Control	ALB gm/dl
0.001	4.05	20	Hepatitis	
	0.8	20	Control	T .bil mg/dl
0.061	0.85	20	Hepatitis	
	1.7	20	Control	AFP ng/ml
0	13.95	20	Hepatitis	
	107.65	20	Control	AFU U/L
0.005	221	20	Hepatitis	
	5.6	20	Control	WBC (x 10^3/dl)
0.534	5.4	20	Cirrhosis	
	243.5	20	Control	Platelets (x 10^3/dl)
0	84	20	Cirrhosis	
	19.5	20	Control	Urea mg/dl
0.683	20.5	20	Cirrhosis	
	0.7	20	Control	creatinine mg/dl
0.008	0.9	20	Cirrhosis	
	4.5	20	Control	ALB gm/dl
0	3.1	20	Cirrhosis	
	0.8	20	Control	T.bil mg/dl
0	1.35	20	Cirrhosis	
	1.7	20	Control	AFP ng/ml
0	11	20	Cirrhosis	
	107.65	20	Control	AFU U/L
0	403.55	20	Cirrhosis	
	5.6	20	Control	WBC (x 10^3/dl)
0.246	5.45	40	HCC	
	243.5	20	Control	Platelets (x 10^3/dl)
0	140	40	HCC	
	19.5	20	Control	Urea mg/dl
0.008	24	40	HCC	
	0.7	20	Control	creatinine mg/dl
0	0.9	40	HCC	
	4.5	20	Control	ALB gm/dl
0	2.1	40	HCC	
	0.8	20	Control	T .bil mg/dl
0	2.7	40	HCC	
	1.7	20	Control	AFP ng/ml
0	3130.5	40	HCC	
	107.65	20	Control	AFU U/L
0	1515.5	40	HCC	

Data are expressed as median range

Table 3: Parametric data among patients groups.

p	Mean	n		
	40.05(4.718)	20	Hepatitis	Age Years
	45.4(5.853)	20	Cirrhosis	
	53.4(7.225)	40	HCC	
0	48.06(8.475)	80	Total	
	4.045(0.3706)	20	Hepatitis	RBCs (x 10^6/dl)
	3.495(0.4989)	20	Cirrhosis	
	3.728(0.5179)	40	HCC	
0.002	3.749(0.5139)	80	Total	
	12.3(0.8663)	20	Hepatitis	Hb gm/dl
	10.53(1.6226)	20	Cirrhosis	
	11.55(1.3832)	40	HCC	
0	11.482(1.4695)	80	Total	
	82.1(8.097)	20	Hepatitis	FBS mg/dl
	86.4(11.659)	20	Cirrhosis	
	90.33(10.598)	40	HCC	
0.017	87.29(10.752)	80	Total	
	78.6(21.967)	20	Hepatitis	AST U/L
	42(10.433)	20	Cirrhosis	
	44.05(12.308)	40	HCC	
0	52.18(21.294)	80	Total	
	105.55(29.726)	20	Hepatitis	ALT U/L
	46.15(13.068)	20	Cirrhosis	
	48.05(14.636)	40	HCC	
0	61.95(31.648)	80	Total	
	92.95(4.548)	20	Hepatitis	Prothrombin concentration %
	63.7(7.299)	20	Cirrhosis	
	53.68(9.124)	40	HCC	
0	66(17.917)	80	Total	
	46.74(3.31224)	20	Hepatitis	Taurine µmol/L
	28.865(3.07661)	20	Cirrhosis	
	16.1473(2.3146)	40	HCC	
0	26.9749(12.91226)	80	Total	
	51.93(6.341)	15	Grade I	Age Years
	51.5(9.434)	12	Grade II	
	56.85(4.688)	13	Grade III	
0.109	53.4(7.225)	40	Total	
	3.64(0.6916)	15	Grade I	RBCs (x 10^6/dl)
	3.825(0.4245)	12	Grade II	
	3.738(0.3595)	13	Grade III	
0.662	3.728(0.5179)	40	Total	
	11.349(1.6961)	15	Grade I	Hb gm/dl
	11.733(1.3852)	12	Grade II	
	11.623(1.0043)	13	Grade III	
0.753	11.55(1.3832)	40	Total	
	91.13(11.747)	15	Grade I	FBS mg/dl
	90.42(11.665)	12	Grade II	
	89.31(8.798)	13	Grade III	
0.906	90.33(10.598)	40	Total	
	40.73(12.527)	15	Grade I	AST U/L
	49(16.192)	12	Grade II	
	43.31(5.483)	13	Grade III	
0.219	44.05(12.308)	40	Total	
	43.07(14.345)	15	Grade I	ALT U/L
	55.83(17.362)	12	Grade II	
	46.62(9.269)	13	Grade III	

0.069	48.05(14.636)	40	Total	
	53.53(8.123)	15	Grade I	Prothrombin concentration %
	58.58(10.022)	12	Grade II	
	49.31(7.532)	13	Grade III	
0.035	53.68(9.124)	40	Total	
	18.6987(0.57335)	15	Grade I	Taurine µmol/L
	15.855(0.50455)	12	Grade II	
	13.4731(0.90823)	13	Grade III	
0	16.1473(2.3146)	40	Total	

Data are expressed as mean ±SD

Table 4: Non parametric data among patients groups.

p	**Median**	**n**		
	5.35	20	Hepatitis	WBC (x 10^3/dl)
	5.4	20	Cirrhosis	
	5.45	40	HCC	
0.939				
	210.5	20	Hepatitis	Platelets (x 10^3/dl)
	84	20	Cirrhosis	
	140	40	HCC	
0				
	21.5	20	Hepatitis	Urea mg/dl
	20.5	20	Cirrhosis	
	24	40	HCC	
0.062				
	0.8	20	Hepatitis	creatinine mg/dl
	0.9	20	Cirrhosis	
	0.9	40	HCC	
0.064				
	4.05	20	Hepatitis	ALB gm/dl
	3.1	20	Cirrhosis	
	2.1	40	HCC	
0				
	0.85	20	Hepatitis	T bil mg/dl
	1.35	20	Cirrhosis	
	2.7	40	HCC	
0				
	13.95	20	Hepatitis	AFP ng/ml
	11	20	Cirrhosis	
	3130.5	40	HCC	
0				
	221	20	Hepatitis	AFU U/L
	403.55	20	Cirrhosis	
	1515.5	40	HCC	
0				
	4.8	15	Grade I	WBC (x 10^3/dl)
	5.7	12	Grade II	
	5.1	13	Grade III	
0.784				
	170	15	Grade I	Platelets (x 10^3/dl)
	75	12	Grade II	
	155	13	Grade III	
0.012				
	24	15	Grade I	Urea mg/dl
	23	12	Grade II	
	24	13	Grade III	
0.614				

	0.9	15	Grade I	creatinine mg/dl
	0.9	12	Grade II	
	1	13	Grade III	
0.802				
	2.1	15	Grade I	ALB gm/dl
	1.8	12	Grade II	
	2.2	13	Grade III	
0.216				
	3.7	15	Grade I	Tbil mg/dl
	2.05	12	Grade II	
	4.2	13	Grade III	
0.392				
	55	15	Grade I	AFP ng/ml
	2568	12	Grade II	
	8521.3	13	Grade III	
0.057				
	1543	15	Grade I	AFU U/L
	1429.5	12	Grade II	
	1520	13	Grade III	
0.584				

Data are expressed as median range

Table 5: Diagnostic Validity Test.

Groups		Cut off	%Sp	%Sen	%PN	%PP	%EFF
HCC Vs non-HCC:	**AFP**	45.9	96.7	82.5	89.2	94.3	91.0
	AFU	764,3	95.0	90.0	93.4	92.3	93.0
	Tau	19.6	100.0	100.0	100.0	100.0	100.0
HCC (G3) Vs (G1&2)	**AFP**	7854.9	85.2	61.5	82.1	66.7	77.5
	AFU	1511	51.9	53.8	70.0	35.0	52.5
	Tau	14.3	100.0	92.3	96.4	100.0	97.5
HCC (G2) Vs (G1)	**AFP**	55	50.0	92.3	87.5	63.2	70.4
	Tau	16.65	100.0	92.3	93.3	100.0	96.3

Data are expressed as percentage

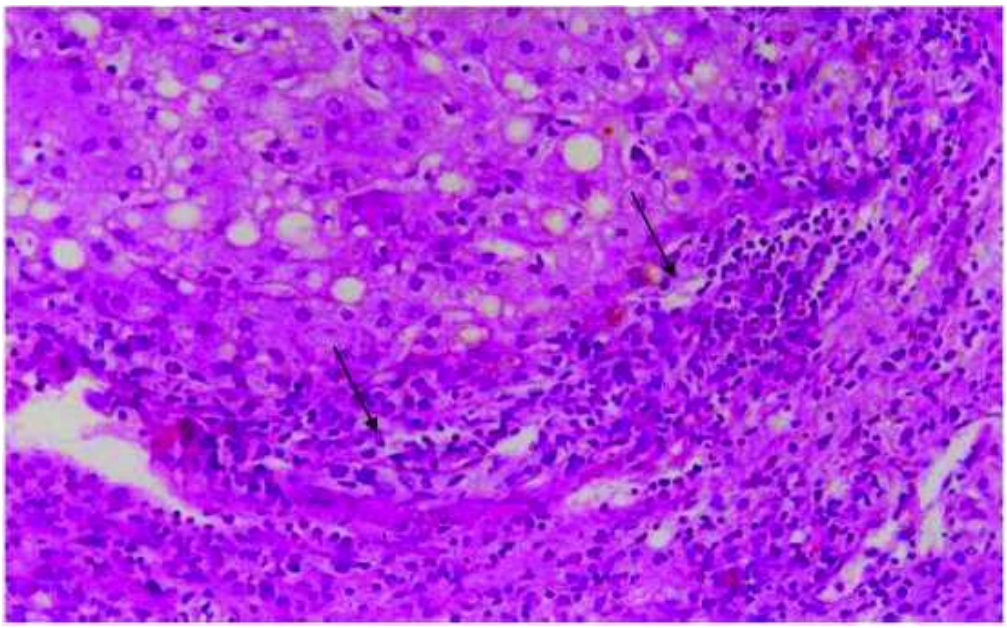

Fig. 1: Liver cirrhosis showing regeneration nodules surrounded by very vascular periportal areas rich in blood capillaries and lymphocytic infiltrate (arrows) H& E xl25.

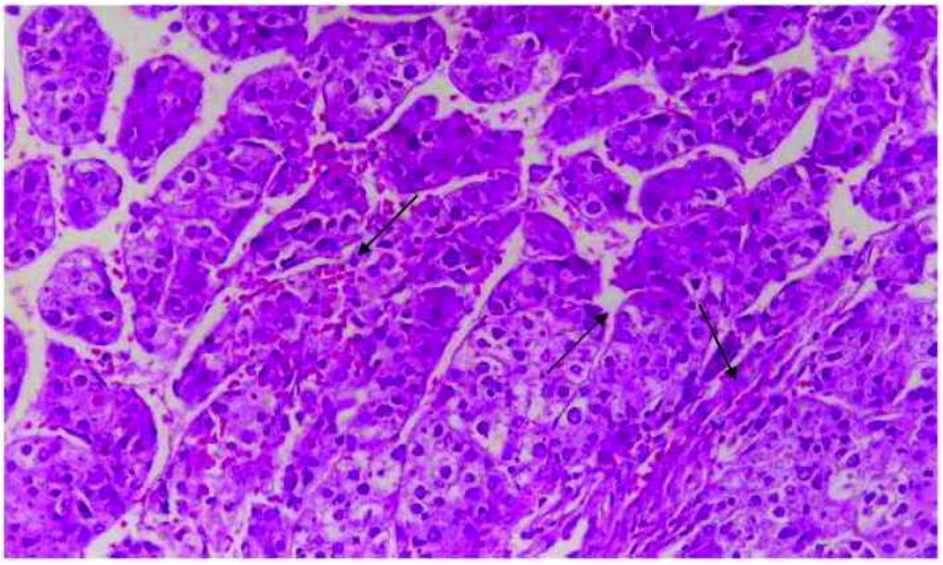

Fig. 2: Hepatocellular carcinoma grade 1 (arrows) H&E stain X125.

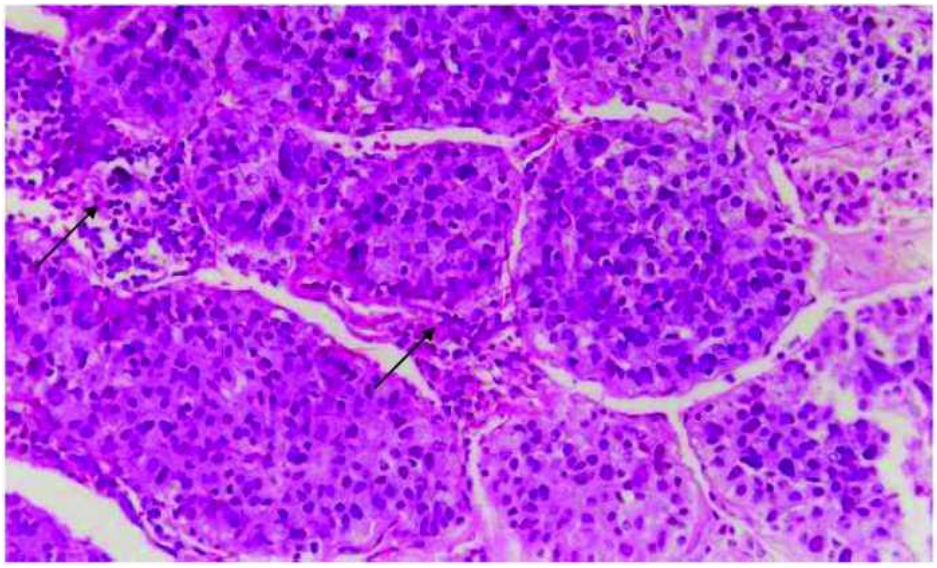

Fig. 3: Hepatocellular carcinoma grade 2, showing vascular stroma (arrows) supporting the tumor cells H&E stain XI25.

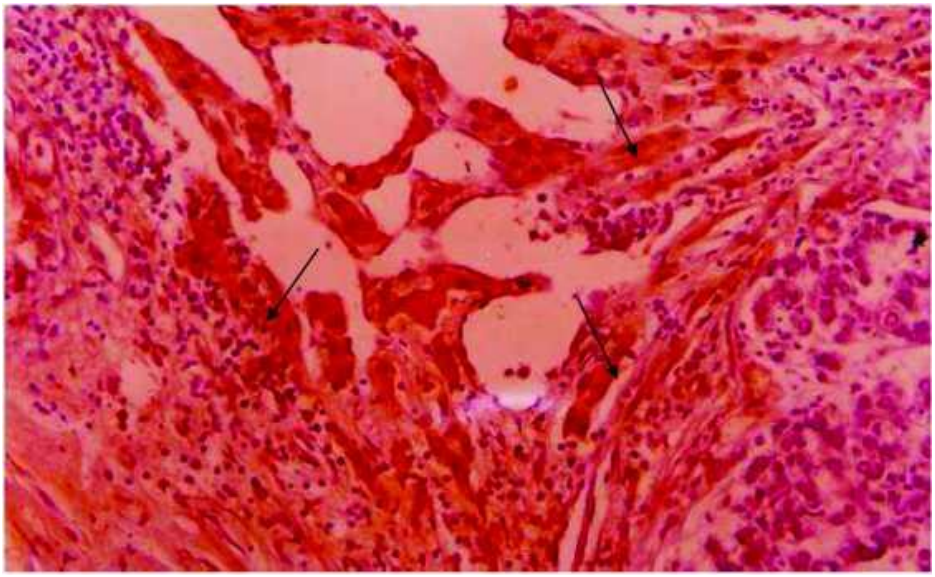

Fig. 4: Hepatocellular carcinoma grade 3, showing highly vascular stroma (arrows) H&E X125.

DISCUSSION

Tumor markers are usually proteins in nature produced by cancer and sometimes by normal cells. Not every person with cancer may have a higher level of tumor marker.[12][18]

Current gold standard and most commonly used biomarkers for HCC patients are AFP and AFU. The current study showed that the serum levels of AFP revealed significant changes compared to normal in chronic hepatitis, cirrhosis and HCC groups and among patients groups. While, AFP (P=0.057) among HCC groups, sensitivity within 61.5-92.3 % and specificity within 50-85.2%. Contrary, several studies have shown that the detection power of AFP for early-stage HCC varies considerably and at a high level, its sensitivity is within the 40-65% range and specificity within the 76-96% range.[12] Concomitantly, AFP as a conventional marker for HCC is frequently undetectable or is only expressed at a very low level when tumor less than 3 cm in size. Furthermore elevated levels of AFP are also seen in chronic hepatitis, cirrhosis and other types of tumors.

In the current study, AFU showed a 4-5-fold increase in serum of chronic hepatitis and cirrhosis patients respectively. Serum level of AFU was markedly increased in the different stages of HCC patients, (P=0.584) were noticed among HCC groups. AFU among HCC groups, sensitivity 53.8% range and specificity 51.9% between grade 3 and grade 1 & 2. Accordingly, AFP and AFU could not be used as early markers for HCC because their levels were extremely elevated only when the carcinogenic architecture present.

Regarding the biochemical analysis, in spite of significant elevation in the levels of both AST and ALT especially in chronic hepatitis and to a lesser extent in cirrhosis and cancer groups but, clinically they still at upper normal range. Confirming our result there are reports of marked fibrosis and even cirrhosis in persons with normal liver enzymes.[19] While serum albumin exhibited a value extremely significant lower than normal about 50% in different of HCC stages, and to a lesser extent 28% in cirrhosis group. On the other hand, prothrombin concentration was significantly decreased in all patients groups with its lowest value recorded in HCC stages patients. Both of bilirubin and prothrombin concentration are important factors in the prognosis of immediate survival in cirrhotic patients.[20] Logically platelets count was extremely decreased in cirrhosis group by about 60% from the normal control. This decrement was sustained in all HCC patients.

But the most impressive observation in this work is the result of antioxidant immune marker taurine, which decreased markedly to about 37% compared to normal control in the serum level of chronic hepatitis patients, which considered as a high-risk group, this lowering in serum taurine was continuously to exhibited value at 28.865 ± 3.07661 µmol/L in cirrhotic group compared to 63.15 ±3.77352 µmol/ L in control group. But the most interesting finding is the level of taurine in the all forty patients after taking liver biopsy from all of them and diagnosed at different stages of HCC was exhibited a values less than 20 µmol/L (18.6987±0.57335 µmol/L in stage one, 15.855±0.5045µmol/L in the second stage, 13.4731±0.90823 µmol/L in the third stage).

So it remains of interest to spotlight on the changes in serum taurine levels in chronic hepatitis patients as risk group than in advanced cirrhosis as highly complicated and in different stages of HCC compared to the normal control level. Notably, we could suspect tumor transformation hepatic patients when serum taurine level ranged between 20-30 µmol/L. Also, one can consider 50 µmol/L serum taurine as a safe margin in all hepatic patients. And when this level ranged between 40-50 µmol/L could be considered as an early sign of liver impairment. But, when the level decreased below 40 µmol/L there will be a higher chance of development of cirrhosis within the following 5-10 years.[21]

So, we could strongly suggest cancer transformation in any hepatic patients has a taurine level below than 20 µmol/L. And this level was continuously decreased according to the HCC stages. The same conclusion was also recorded in cancer breast and uterus.[12][13] It is well known that chronic hepatitis C infection represent the most common cause of hepatic fibrosis in Egypt and those patients are at high risk for cirrhosis and HCC. Transient elastography (TE) using fibroscan is a relatively recent non-invasive method useful for staging of hepatic cirrhosis.[22][23] It assesses the different degree of liver fibrosis into 5 stages from F0-F4. **In 2017** serum taurine level was used in comparison to fibroscan for early diagnosis of liver fibrosis in Egyptian patients infected with HCV.[16] The authors noticed that when the fibroscan diagnosis patients at stage zero of stiffness F0 usually regular checkup is the only advice from the doctor to all patients. But, in contrast, the most impressive observation is the antioxidant taurine showed a highly significant decrease in their serum levels, which can be considered as an early sign of liver impairment. This level was continuously decreasing parallel to the degree of fibrosis. These may encourage the authors to suggest that the assessment of taurine level in sera of all hepatic patients beside fibroscan is of great value in the early diagnosis of any fibrotic changes in the liver. Epidemiologic studies demonstrated that diabetic patients are more likely to develop cancer, which is mainly due to immune depression.[24] Contrary, it was suggested that taurine play an important role in initiation and progression of the immune response.[25] So, recently serum taurine level was used as a pre-early marker for diabetic complication especially in diabetic retinopathy and diabetic foot.[14][15] Supporting our result, the previous authors considered 20µmol/L of taurine is a cut off value for different types of cancer in diabetic patients. This may encourage us to suggest that taurine is a highly sensitive nonspecific tumor marker. In the HCC

patients, the current study revealed that serum taurine is 100 % specific and sensitive marker to discriminate HCC from non HCC patients.

Moreover, a lot of researchers through light on the use of taurine as an antineoplastic drug in different types of cancers, like cancer bladder,[26] gastrointestinal tract[27] and as a biomarker in non-muscle invasive bladder cancer.[28] Recently, it was suggested that a combination of curcumin and taurine may be a noval prophylactic agent against hepatocarcinogenesis.[29]

Although the hepatoprotective properties of taurine are well established, however, the correlation of the preoperative serum level of this amino acid in both donor and recipient of LDLT and graft function has not been investigated so far. In 2005,[30] Schemmer et al found for the first time that in vivo taurine minimizes reperfusion injury after liver transplantation in rats. Decreased leukocyte–endothelial cell interaction and improved microcirculation are the proposed mechanisms, which are most likely Kupffer cell–dependent.

CONCLUSION

We suggest the assessment of serum taurine level for all hepatic patients as a pre-early marker of HCC and may have a rule in identifying ESLD patients candidate for LDLT, an area which needs further research.

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AUTHOR CONTRIBUTIONS

Ibrahim M. EL-Agouza, Mohamed M. Abdel Ghaffar, Hanaa A. El Gendy have full access to all the data in the study and take responsibility for the integrity of the data. Study concept and design: Ibrahim M. EL-Agouza, Mohamed M. Abdel Ghaffar, Afaf A. Abd-Allah. Acquisition of data: Hanaa A. El Gendy, Afaf A. Abd-Allah Kholod H. Taha. Analysis and interpretation of data: Ibrahim M. EL-Agouza, Mohamed M. Abdel Ghaffar, Afaf A. Abd-Allah.. Drafting of the manuscript: Ibrahim M. EL-Agouza, Mohamed M. Abdel Ghaffar, Hanaa A. El Gendy. Critical revision of the manuscript for important intellectual content: Ibrahim M. EL-Agouza, Mohamed M. Abdel Ghaffar, Hanaa A. El Gendy, Afaf A. Abd-Allah, Kholod H. Taha.

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Compliance with Ethical Requirements

Conflicts of interest

All authors declare that they have no conflicts of interest.

Ethical approval

The study protocol was approved by the local research ethics committee (HAM00077) and by local health development which conformed to the Egyptian National guidelines.

Informed consent

Written informed consent was obtained from the patients or their surrogates upon their enrolment in the study.

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