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Serum Squamous Cell Carcinoma Antigen Level in Cirrhotic Chronic Hepatitis C Patients With and Without Hepatocellular Carcinoma

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Abstract

This study will be carried out on 500 personnel divided into five groups: Group A: 100 cases of hepatocellular carcinoma without interventions. Group B: same 100 cases of group A before and 3 months after successful interventions.Group C: 100 cases of established cirrhosis. Group D: 100 cases with chronic hepatitis C virus infection without established cirrhosis. Group E: 100 healthy individuals as controls.

Methods: Sera from selected patients and controls have been used for estimation of SCC-Ag using CanAg SCC EIA.

Results: high significant increase in serum SCCA level in patients with HCC (groupA and groupB) when compared to cirrhotic, chronic HCV and control groups ($P < 0.001$). Positive significant correlation was found between AFP and serum SCCA level .The best cut-off value to differentiate HCC patients from cirrhotic patients was 3.2 ng/ml for SCCA yielded with 80% sensitivity and 90% specificity. When combined sensitivity of both markers was calculated in our study at the best-chosen cutoff values (SCCA 3.2 ng/ml and AFP 200 ng/ml) sensitivity improved to 93%.

Conclusion: Combined SCCA and AFP can be used as in diagnosis of HCC and follow up 3 months after therapeutic intervention.

Key words: Hepatocellular carcinoma; Squamous cell carcinoma antigen; Alfa feto protein

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver. HCC is the fifth most common malignancy in the world and the third most common cause of cancer related deaths worldwide. It is a major health problem in Egypt with the incidence expected to rise continuously in the next decade.[1-2]

The diagnosis of liver cancer depends on both screening with alpha-fetoprotein (AFP) and radiological imaging studies. Generally, normal levels of AFP are below 10 ng/ml but AFP greater than 200 ng/ml is suggestive of HCC . The sensitivity of AFP for liver cancer is about 67%; therefore a normal AFP does not exclude HCC. Searching another tumor marker, that together with AFP could improve the diagnostic utility of HCC.[3]

Squamous cell carcinoma antigen (SCCA), a member of the high molecular weight family of serine protease inhibitors named serpins which are physiologically found in the granular layers of normal squamous epithelium but found to be typically expressed by neoplastic cells of epithelial origin in a number of different cancers for example cancer cervix, lung, and head and neck cancers hence, it can be used as a clinical marker of these malignancies.[4]

The structure of the serpin ovalbumin revealed the archetype native serpin fold that typically have three β-sheets (termed A, B and C) and eight or nine α-helices (hA-hI). Serpins also possess an exposed region termed

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the reactive centre loop (RCL) that includes the specificity determining region and forms the initial interaction with the target protease.

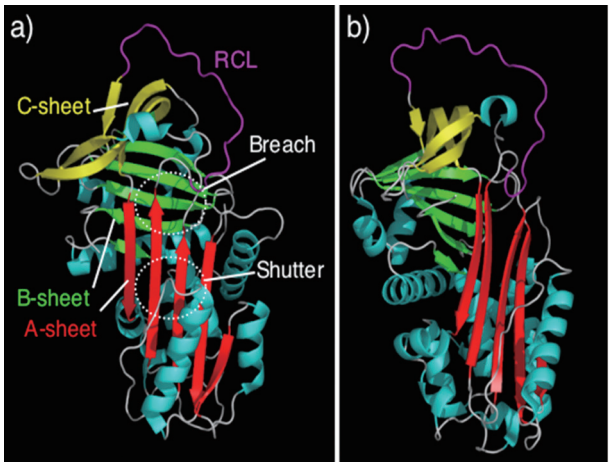

Figure 1
Structure of Serine Protease Inhibitor and Squamous Cell Carcinoma Antigen (SCCA)

Note. a)The X-ray crystal structure of native serine protease inhibitor ; The five-stranded A-sheet is in red, the six-stranded B-sheet in green, and the four-stranded C-sheet in yellow. α-helices are shown in cyan. The RCL is at the top of the molecule in magenta. Two functionally important regions of the serpin, the breach and the shutter, are labeled. b) The structure of squamous cell carcinoma antigen (SCCA).

Recently much attention has been focused on the role of SCCA in HCV cirrhotic patients suggesting that high levels of SCCA can assess HCC development.[5]

The aim of this study was to assess the serum level of squamous cell carcinoma antigen (SCCA) in cirrhotic chronic HCV patients with and without hepatocellular carcinoma in relation to alfa feto protein (AFP).

AIM OF THE WORK

The aim of this study was to assess the serum level of squamous cell carcinoma antigen (SCCA) in cirrhotic chronic HCV patients with hepatocellular carcinoma in relation to alfa feto protein (AFP) .

PATIENT AND METHODS

These groups were from both sexes who are admitted to the inpatient ward and the outpatient clinic of Tropical Medicine Department, Faculty of Medicine, Alexandria University.

This study was carried out on :

Group A: 100 cases of hepatocellular carcinoma without interventions.

Group B: same 100 cases of group A before and 3 months after successful interventions.

Group C: 100 cases of established cirrhosis.

Group D: 100 cases with chronic hepatitis C virus infection without established cirrhosis.

Group E: 100 healthy individuals as controls.

All patients in this study were subjected to: complete blood picture, liver biochemical profile, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum alkaline phosphatase, total and direct serum bilirubin, prothrombin time and activity, serum albumin blood urea nitrogen(BUN), serum creatinine. Fasting blood sugar. Serum alpha fetoprotein (AFP).

Determination of squamous cell carcinoma antigen (SCC-Ag) Sera from selected patients and controls were used for estimation of SCC-Ag using CanAg SCC EIA. The CanAg SCC EIA is a solid phase, non-competitive immunoassay based upon the direct sandwich technique. Calibrators and patient samples are incubated together with biotinylated Anti-SCC monoclonal antibody in Streptavidin coated microstrips. After washing buffered Substrate/Chromogen reagent (hydrogen peroxide and 3, 3', 5, 5' tetra-methylbenzidine) is added to each well and the enzyme reaction is allowed to proceed. During the enzyme reaction a blue colour will develop if antigen is present. The intensity of the colour is proportional to the amount of SCC present in the samples. The colour intensity is determined in a microplate spectrophotometer at 620 nm (or optionally at 405 nm after addition of Stop Solution). Calibration curves are constructed for each calibrator. The SCC concentrations of patient samples are the read from the calibration curve.

STATISTICAL ANALYSIS

Statistical analysis was done using the SPSS software package version 20.0

Statistical analysis was done to obtain the mean, the standard deviation; the standard error of each mean and for comparison between the different groups involved in this study ONE WAY test was used for comparison between independent samples.

Arithmetic mean ($\overline{X}$) was calculated as follows:

$$\overline{X} = \frac{\sum X}{n}$$

Where: $\overline{X}$= the arithmetic mean,
$\sum X$= the sum of observations,
n= the number of observations.

Standard deviation (SD) was calculated as follows:

$$SD = \sqrt{\frac{\sum (X - \overline{X})^2}{n-1}}.$$

Where: n= the number of cases, X=individual values, $\overline{X}$= the arithmetic mean of the group.

Student (t) test:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{(S.E_1)^2 + (S.E_2)^2}}.$$

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Where: $\overline{X}_1$ = Arithmetic mean of the 1st group,
$\overline{X}_2$ = Arithmetic mean of the 2nd group ,
*S.E*1 = Standard error of the 1st group,
*S.E*2 = Standard error of the 2nd group.

Chi-square (X2):

For comparison between distribution of patients according to different items of study and use this formula for calculation:

$$X^2 = \sum \frac{(O-E)^2}{E}$$

O = Observed results, *E* = Expected results

(*O*-*E*)2 = Difference squared

Where: $E = \frac{\text{Total row x total column}}{\text{Grand total}}$

The probability "*p*" value:

It was obtained from special table for probability (*p*) value, where the degree of freedom (*n*1+ *n*2 – 2) was used.

Where:

*n*1 = Number of observations of the first group (the control group)

*n*2 = Number of observations of the second group (the patients group)

A "*p*" value of less than 0.05 was considered statistically significant.

Table 1 shows a statistical significant difference between different studied groups regarding alpha feto protein *(P*= 0.000).

Table 1
Comparison Between Different Studied Groups Regarding Alpha Feto Protein

	Mean	Std. deviation	Minimum	Maximum
Gp. A	263.0	96.02	150.	438
Gp. B	209.4	64.7	145.	380.
Gp. C	154.5	48.16	75.	210.
Gp. D	7	1.82574	5	9
Gp. E	1.22	0.27406	0.8	1.6
F		38.208		
P		0.000*		

Table 2 shows a statistical significant difference between different studied groups regarding SCCA level (*P*= 0.000).

Table 2
Comparison Between Different Studied Groups Regarding SCCA Score

	Mean	Std. deviation	Minimum	Maximum
Gp. A	5.53	2.16	2.5	10.
Gp. B	5.3	1.5	3.3	7.6
Gp. C	3.3	1.6	1.2	5.6
Gp. D	0.824	0.15897	0.6	1.05
Gp. E	0.646	0.23172	0.3	0.95
F		28.897		
P		0.000*		

Also, Positive significant correlation was found between AFP and SCCA in both groups

Table 3
Correlation Between AFP and SCCA

		AFP	
		HCC without intervention	HCC with intervention
SCCA	*r*	0.629*	0.525*
	p	<0.001	<0.001

Note. *r*: Pearson coefficient , *: Statistically significant at $p \leq 0.05$

When combined sensitivity of both markers were calculated in our study at the best-chosen cutoff values (SCCA 3.2 ng/ml and AFP 200 ng/ml) sensitivity improved to 93%. (Table 4)

Table 4
AUC for AFP, SCCA and SCCA + AFP

	AUC	*p*
AFP + SCCA	0.930*	0.001
AFP	0.890*	0.003
SCCA	0.820*	0.016

DISCUSSION

In the present study patients with HCC either with or without therapeutic intervention have significantly higher level of AFP in comparison to chronic HCV, cirrhotic and control groups this is in agreement with Awadallah et al.[6] who reported a statistically highly significant elevation in the serum AFP in HCC group when compared with control group. Moreover, the mean serum level of AFP in group A (HCC before intervention) was 263 ng/ml that decreased to 209.4 ng/ml in group B after therapeutic intervention and this agreed with Feng et al[7] and Molinari et al.[8] Also, at AFP level of 200 ng/ml, the sensitivity was 90%, while the specificity was 60%.

Our results showed that SCCA level ranged from 2.5–10 with a mean of 5.53 in HCC patients without interventions, 3.3–7.6 with a mean of 5.3 in patients with HCC with therapeutic interventions, 1.2–5.6 with a mean of 3.3 in cirrhotic group, 0.6–1.05 with a mean of 0.824 in chronic HCV group while healthy control group had much lower values ranging from 0.3–0.95 with a mean of 0.646. Thus, a highly significant increase in serum SCCA level in patients with HCC before and after therapeutic intervention when compared to cirrhotic, chronic HCV and control groups ($P < 0.001$). These results were in accordance with Hussein et al. [9] and El Ezawy et al.[10] SCCA was also higher among patients with HCC before intervention compared to patients with HCC after intervention as found by Bin et al.[11]

Applying the ROC curves analysis showed the best cut-off value to differentiate HCC patients from cirrhotic patients was 3.2 ng/ml for SCCA yielded 80% sensitivity and 90% specificity. These results were in agreement with Trevisani et al.[12]

Patients with HCC, in our study were none randomized selected as BCLC stage B (either one HCC lesion < 5 cm

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in size or 3 lesions < 3 cms) so no statistical correlation was done between serum AFP level and tumor size.

Our results showed a significant positive correlation between serum SCCA and AFP among patients with HCC before and after therapeutic intervention. Our data are in agreement with that of Hussein et al.[9] and El Ezawy et al.[10] who detected that SCCA were positively significantly correlated with AFP level.

When combined sensitivity of both markers was calculated in our study at the best-chosen cutoff values (SCCA 3.2 ng/ml and AFP 200 ng/ml) sensitivity improved to 93%. Matching results were found by Gianluigi et al.[4]

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APPENDIX: LIST OF ABBREVIATIONS

AFP	:	Alpha-feto protein
AFP-L3	:	Lens culinaris agglutinin-reactive fraction of AFP.
AUC	:	Area under the curve
HCC	:	Hepatocellular carcinoma.
HCV	:	Hepatitis C virus.
SCCA	:	Serum squamous cell carcinoma antigen
TACE	:	Transarterial chemoembolization

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