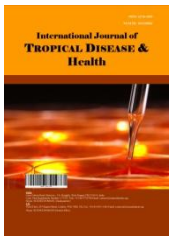

International Journal of TROPICAL DISEASE & Health

43(10): 19-26, 2022; Article no.IJTDH.84923
ISSN: 2278–1005, NLM ID: 101632866

Study of Selenoprotein P as a Marker of Hepatocellular Carcinoma Diagnosis and Therapeutic Intervention Outcome

Yara Mohamed Elqatary [a*], Mona Ahmed Helmy Shehata [a], Amany Mohamed Abo Elenein [b] and Lobna Ahmed Fahmy Abo Ali [a]

[a] Tropical Medicine and Infectious Diseases Department, Faculty of Medicine, Tanta University, Tanta, Egypt.
[b] Clinical Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2022/v43i1030618

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/84923

Original Research Article

Received 07 February 2022
Accepted 11 April 2022
Published 14 May 2022

ABSTRACT

Background: Hepatocellular carcinoma is the main public health issue on a global scale, and its diagnosis remains difficult. HCC is now believed to be a common malignancy and a foremost cause of death in Egypt, owing to the high prevalence of cirrhosis associated with chronic HCV. Its incidence has increased in recent years, and it is expected that there will be continuous a rise in the number of occurrences. This study aimed to evaluate the role of serum selenoprotein P as a marker for diagnosis and follow up of therapeutic intervention outcome in hepatocellular carcinoma patients.
Methods: This was a prospective study that took place in Tropical medicine department, Tanta university. Seventy patients with cirrhosis of the liver were included, either with or without hepatocellular carcinoma. The studied patients were divided into group I A of 20 HCC patients who underwent HCC therapeutic intervention, those patients were evaluated before and after their therapeutic intervention, group I B of 25 HCC patients who did not undergo HCC therapeutic intervention as unsuitable and group II of 25 patients with liver cirrhosis as controls
Results: Selenoprotein P was decreased significantly in group IB than group IA and group II (P <0.001) and was significantly decreased in group IA than group II (P <0.001). At cut-off <11 ng/ml

**Corresponding author: Email: thesismse@gmail.com;*

selenoprotein P can differentiate between HCC and liver cirrhosis with 80% sensitivity, 76% specificity, 85.7% PPV, 67.9% NPV and 0.851 AUC. After therapeutic intervention, increased serum level of selenoprotein P can be an indicator of good response to treatment. While decreased serum selenoprotein P level can be an indicator of poor response (P <0.001).

Conclusions: Serum selenoprotein P could be useful as a possible diagnostic biomarker for HCC. Detecting that biomarker in serum is a simple, non-invasive procedure that is more realistic than measuring it in tissue samples procured only through procedures that are invasive. Selenoprotein P could be used as a predictive marker of better therapeutic intervention outcome in hepatocellular carcinoma patients. Additionally, our findings imply that Se may be utilised as a supportive treatment for HCC by influencing the level of selenoprotein P.

Keywords: Hepatocellular carcinoma; liver cirrhosis; selenoprotein P; therapeutic intervention outcome.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is a public health issue in Egypt. It is responsible for 70.48 % of liver tumours in their entirety .(primary & secondary liver tumors) by many of Egyptians, it is the second most prevalent type of cancer after bladder cancer in men and breast cancer in women, and it is also the second main cause of death in men [1]. Globally, HCC carcinogenesis is a complicated process, multifactorial, multistep process that is related to a history of chronic liver diseases. Persistent hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, as well as alcohol and aflatoxin consumption, are widely recognised as causative factors [2].

The high morbidity rate associated with HCC is primarily due to a dearth of early detection indicators and a poor prognosis. As a result, novel frontiers in HCC diagnosis and treatment continue to be Priority areas of research [3]. Rapid detection and efficient treatment are critical for patients with HCC to improve their survival and quality of life. Since the 1970s, AFP has been used as a primary diagnostic serum biomarker for HCC. However, due to its low sensitivity and specificity, serum AFP level is not a potential biomarker of HCC [4]. Even in patients with advanced HCC, the AFP level may remain normal in 15~30% of the patients [5]. As a result, for HCC diagnosis, a unique serum biomarker with superior diagnostic validity is necessary.

Selenium is an essential trace element that has a critical role in cancer prevention. In the human body, selenium has various functions in a diverse range of selenium-containing proteins. Of these proteins, selenium-binding protein P (SELENOP) is a possible mediator of the anticancer functions [6]. The liver retains the majority of selenium absorbed and recirculates it as a component of SELENOP [7]. The selenium-binding protein, which is followed by detoxification pathways in an indirect manner, was found to be significantly down-regulated in patients with HCC. The protein's cellular importance appears to be related to its ability to store selenium, which is required for the function of a large number of detoxification enzymes. The decrease in selenium-binding protein expression in HCC may be significant., because it has a direct effect on selenium's ability to regulate cell function and growth in HCC, as has been previously disclosed for ovarian, lung, and colon carcinoma [8], Indeed, successful HCC management has been proposed through the use of dietary antioxidants and micronutrients [9].

Previous studies indicate that SELENOP down regulation is followed by poor prognosis in various cancers [10]. Decreased concentrations of selenium in HCC tumour tissues were associated with an increase in the grade of progressive cancer [11].

The purpose of this study was to determine the role of serum selenoprotein P as a marker for diagnosis and follow up of therapeutic intervention outcome in hepatocellular carcinoma patients.

2. PATIENTS AND METHODS

This was a prospective study performed on 70 cases who were enrolled from inpatients and outpatient's clinic of Tropical Medicine Department: Faculty of Medicine, Tanta University from December 2018 to April 2020.

Liver cirrhosis patients with or without hepatocellular carcinoma were included, while patients suffering from; cardiovascular diseases,

diabetes mellitus, systemic hypertension, other malignancies rather than HCC were excluded.

All patients had been exposed to the following: Full history taking including, complete clinical examination, routine laboratory investigations such as Complete blood count, erythrocyte sedimentation rate, renal function tests (serum creatinine and blood urea), liver biochemical tests (ALT, AST, INR, serum bilirubin, serum albumin), viral hepatitis markers: HBsAg, HBc antibody, HCV antibody, alpha-fetoprotein, estimation of serum selenoprotein P using ELISA technique.

2.1 Sampling

All patients were asked for the sample first, then 3 ml venous blood sample was taken by a disposable plastic syringe under complete aseptic conditions. The kit is for the determination of level of Human SELENOP in the sample quantitively, apply purified SELENOP antibody to coat microtiter plate, render solid-phase antibody, then insert SELENOP to wells, Combine SELENOP antibody with labelled Horseradish Peroxidase (HRP) to form antibody-antigen -enzyme-antibody complex. After complete washing, introduce Tetramethylbenzidine (TMB) substrate solution, TMB substrate becomes blue at HRP enzyme catalysed. The reaction is ended by the addition of a stop solution, and the colour change is quantified using a 450 nm wavelength. The concentration of SELENOP in the samples is then measured comparing the optical density (O.D.) of the samples to the standard curve.

Radiological investigation: Pelvi-abdominal ultrasound and pelvi-abdominal Triphasic CT for diagnosis of hepatocellular carcinoma.

2.2 Statistical Analysis

The Statistical Package for the Social Sciences version 25 was applied to conduct the statistical analysis (IBM Inc., Chicago, IL, USA). Shapiro-Wilks test for normality and to determine the distribution of quantitative variables, histograms were used to determine the appropriate type of statistical testing.: parametric or nonparametric. The significance level was set to p0. 05. Two groups: Quantitative parametric variables were presented as mean and standard deviation (SD). They were compared between the two groups by unpaired student's t- test. Three groups: parametric variables were expressed as mean and standard deviation (SD) and were compared using F test among the three groups with post hoc (LSD) test to compare each two groups.

3. RESULTS

Right hypochondrial pain was significantly higher in group IA and IB in comparison to group II (P <0.001) and encephalopathy was significantly higher in group IB than the two other groups (P = 0.022). The age, sex, smoking, hepatomegaly and splenomegaly insignificantly different among the three groups. Selenoprotein P was decreased significantly in group IB than group IA and group II and was significantly decreased in group IA than group II (P <0.001) Table 1.

Table 1. Patients' characteristics and selenoprotein P of the studied groups

		Group IA (n = 20)	Group IB (n = 25)	Group II (n = 25)	P value		
Age (years)		57.65 ± 10.50	58.56 ± 8.77	56.64 ± 11.36	0.804		
Sex	Male	15 (75%)	20 (80%)	16 (64%)	0.431		
	Female	5 (25%)	5 (20%)	9 (36%)			
Smoking		8 (40%)	16 (64%)	11 (44%)	0.21		
Clinical findings	Hepatomegaly	0 (0%)	1 (4%)	0 (0%)	0.401		
	Splenomegaly	11 (55%)	17 (68%)	13 (52%)	0.481		
	Right hypochondrial pain	20 (100%)	21 (84%)	0 (0%)	<0.001*		
	Encephalopathy	0 (0%)	4 (16%)	0 (0%)	0.022*		
Selenoprotein P ng/ml		10.11 ± 1.26	8.73 ± 1.29	11.43 ± 0.62	<0.001*	P1	<0.001*
						P2	<0.001*
						P3	<0.001*

*Data are presented as mean ± SD or frequency (%). * Significant as P value < 0.05, P1: P value between group IA and group IB, P2: P value between group IA and group II, P3: P value between group IB and group II.*

Selenoprotein P at cut-off <11 ng/mL can differentiate between group I and group II with 80% sensitivity, 76% specificity, 85.7% PPV, 67.9% NPV and 0.851 AUC Fig. 1.

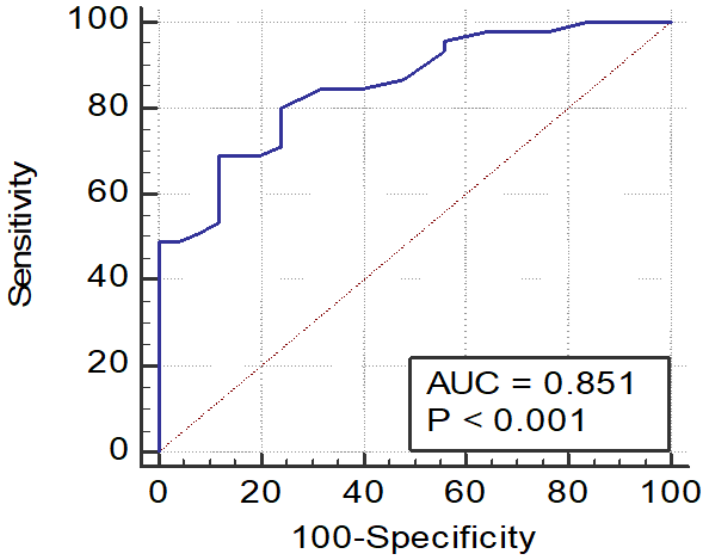

Fig. 1. Diagnostic performance of selenoprotein P for HCC detection

Table 2 shows Therapeutic intervention outcome among HCC patients group IA

Table 2. Therapeutic intervention outcome among HCC patients group IA

Therapeutic intervention	Complete ablation / response n (%)	Partial ablation / Response n (%)	Progressive course n (%)
Microwave ablation	3	5	
Radiofrequency ablation	3	2	
Transarterial chemoembolization	1	2	2
Surgical resection	1	1	
Total n (%)	8 (40%)	10 (50%)	2 (10%)

There were insignificant correlations between selenoprotein P and AFP in group IA before and after therapeutic intervention
Table **3**.

Table 3. Correlation between selenoprotein P and AFP in group IA before and after the therapeutic intervention

	Before therapeutic intervention	After therapeutic intervention
r	-0.022	0.119
P value	0.927	0.618

r: # Coefficient of correlation

There was an insignificant difference between complete response and partial response or progressive course patients. There was a significant increase in serum selenoprotein P among patients showing complete response compared to those with partial response or progressive course (P <0.001). There was an insignificant difference between complete response and partial response or progressive course patients and significant increase of serum AFP in partial response or progressive course group compared to complete response group (P =0.031) Table 4.

Table 4. Selenoprotein P and AFP before and after therapy in relation to the therapeutic intervention outcome among HCC patients group IA

		Complete response (n = 8)	Partial response or progressive course (n = 12)	P value
Selenoprotein P	Before	9.89±1.31	10.08±1.34	0.761
ng/ml	After	12.75±1.21	6.73±0.61	<0.001*
	T	2.86±1.20	-3.35±1.31	<0.001*
AFP	Before	8.22 (2.7-143)	26.25 (3.5-135)	0.076
ng/ml	After	6.38 (2-440)	50.6 (4.2-800)	0.031*
	Z	-1.23 (-11.53: 279)	19.75 (-91.6:796.5)	0.090

Data are presented as mean ± SD or median (range)

4. DISCUSSION

We aimed in the current study to assess the function of serum selenoprotein P as a marker for diagnostic evaluation and follow-up of therapeutic intervention outcome in hepatocellular carcinoma patients. Right hypochondrial pain was significantly higher in group IA (100%) and IB (84%) compared to group II (0%). This was consistent with Barghini et al.,2013 who reported that, abdominal pain is frequent in 95% of HCC patients [12]. In the present work, encephalopathy was significantly higher in group IB than the two other groups. Our findings were supplemented by Hung et al., [13] who found that, hepatic encephalopathy is one of the three major complications of HCC.

In this research, selenoprotein P was reduced significantly in group IB than group IA and group II and was significantly decreased in group IA than group II. This was in harmony with Tarek et al.,2017 who demonstrated that, serum SELENOP concentrations were significantly lower in HCC cases in comparison to both chronic liver disease cases and healthy controls [14]. In this research, SELENOP revealed a significant reduction in HCC patients of group IA and group IB compared to cirrhotic patients of group II. According to Rizk et al. [15], SELENOP levels were significantly lower in HCV-infected patients than in healthy controls.

In the current study, at cut-off <11 ng/ml Selenoprotein P can differentiate between HCC and liver cirrhosis with 80% sensitivity, 76% specificity, 85.7% positive predictive value, 67.9% negative predictive value and 0.851 area under the curve.

Tarek et al., [14] demonstrated that, SELENOP could be an independent predictor of HCC risk. The best cut-off for selenoprotein P to differentiate hepatocellular carcinoma group from chronic liver disease (CLD) and healthy control groups was 4.30 mg/L.

In the present work, HCC patients who underwent HCC therapeutic intervention were (20); 8 patients with microwave ablation, 5 patients with radiofrequency ablation, 5 patients with transarterial chemoembolization and 2 patients with surgical resection of the tumors. Out of them 8 patients (40%) show complete response to the therapeutic intervention (well ablated hepatic focal lesion), 10 patients (50%) show partial tumor ablation and 2 (10%) patients show progressive disease with a metastatic course. Lo et al., 2002 reported that, out of 29 HCC patients underwent chemoembolization, there were 9 of complete responses, 12 of partial responses, 1 stabilization, and 7 patients showed progressions [16].

As regards the relationship between selenoprotein P and the therapeutic intervention outcome in HCC, there was a significant rise in the percentage of patients with perfect response versus those with incomplete response or progressive course. So, the current study revealed that the post interventional increased level of serum selenoprotein P could be used as a predictive marker of better therapeutic intervention outcome in hepatocellular carcinoma patients.

After therapeutic intervention, increased serum level of selenoprotein P with a mean of (2.86±1.20) can be an indicator of good response to treatment. While decreased serum selenoprotein P level with a mean of (-3.35±1.31) can be an indicator of poor response.

Our results were supported by fact reported by Burk et al.,[17] that liver transplantation caused a rise in selenoprotein P concentration. This indicates that the decline in selenoprotein P in liver disease is reversed by improvement in hepatic function.

Rizk et al.'s [15] study also reported a significant rise in selenoprotein P levels in the HCV group following treatment with direct-acting antiviral agents compared to the HCV group prior to treatment (DAAs).

Furthermore, in this work, AFP showed insignificant change after the therapeutic intervention, as many of group IA patients showed pre- interventional average AFP levels in contrary to selenoprotein P levels that showed a significant relationship to the therapeutic intervention outcome. According to the present results selenoprotein P level could be beneficial as a diagnostic marker for HCC diagnosis and therapeutic intervention outcome follow up especially in cases with average AFP.

Recommendation: we can recommend the determination of serum selenoprotein P as a diagnostic biomarker for HCC. Serum selenoprotein P could be beneficial as a biomarker for HCC therapeutic intervention outcome follow up especially in cases with

average AFP. Serum selenoprotein P may be a new biomarker for assessing liver function. Selenium supplementation for patients with chronic liver diseases. Additional large-scale studies are necessary to corroborate our findings.

5. CONCLUSIONS

The present study suggests that serum selenoprotein P could considered as a possible biomarker for the diagnosis of HCC. Detecting that biomarker in serum is a simple, non-invasive procedure that is more feasible than detecting it in tissue samples through invasive techniques. Selenoprotein P could be used as a predictive marker of better therapeutic intervention outcome in hepatocellular carcinoma patients. Additionally, our observations suggest that it may be used as a supportive therapy for HCC by affecting the level of selenoprotein P.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

Ethical committee approval was taken prior to starting to collect the cases from Tanta University (32578/09/18), and approval from all patients was taken before doing any maneuver.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Baghdady I, Fouad F, Sayed M, Shoaib A, Salah Y, Elshayeb E, et al. Serum markers for the early detection of hepatocellular carcinoma in patients with chronic viral hepatitis C infection. Menoufia Med J. 2014;27:544-51.
2. Wei Z, Doria C, Liu Y. Targeted therapies in the treatment of advanced hepatocellular carcinoma. Clin Med Insights Oncol. 2013;7:87-102.
3. Callegari E, Gramantieri L, Domenicali M, D'Abundo L, Sabbioni S, Negrini M. MicroRNAs in liver cancer: a model for investigating pathogenesis and novel therapeutic approaches. Cell Death Differ. 2015;22:46-57.
4. Ertle JM, Heider D, Wichert M, Keller B, Kueper R, Hilgard P, et al. A combination of α-fetoprotein and des-γ-carboxy prothrombin is superior in detection of hepatocellular carcinoma. Digestion. 2013;87:121-31.
5. El-Serag HB, Kramer JR, Chen GJ, Duan Z, Richardson PA, Davila JA. Effectiveness of AFP and ultrasound tests on hepatocellular carcinoma mortality in HCV-infected patients in the USA. Gut. 2011;60:992-7.
6. Pol A, Renkema GH, Tangerman A, Winkel EG, Engelke UF, de Brouwer APM, et al. Mutations in SELENBP1, encoding a novel human methanethiol oxidase, cause extraoral halitosis. Nat Genet. 2018;50:120-9.
7. Burk RF, Hill KE. Regulation of Selenium Metabolism and Transport. Annu Rev Nutr. 2015;35:109-34.
8. Corona G, De Lorenzo E, Elia C, Simula MP, Avellini C, Baccarani U, et al. Differential proteomic analysis of hepatocellular carcinoma. Int J Oncol. 2010;36:93-9.
9. Halliwell B. Free radicals and antioxidants - quo vadis? Trends Pharmacol Sci. 2011;32:125-30.
10. Huang C, Ding G, Gu C, Zhou J, Kuang M, Ji Y, et al. Decreased selenium-binding protein 1 enhances glutathione peroxidase 1 activity and downregulates HIF-1α to promote hepatocellular carcinoma invasiveness. Clin Cancer Res. 2012;18:3042-53.
11. M DIS, Volpe MG, Colonna G, Nazzaro M, Polimeno M, Scala S, et al. A possible predictive marker of progression for hepatocellular carcinoma. Oncol Lett. 2011;2:1247-51.
12. Slotta JE, Kollmar O, Ellenrieder V, Ghadimi BM, Homayounfar K.

Hepatocellular carcinoma: Surgeon's view on latest findings and future perspectives. World J Hepatol. 2015;7:1168-71.
13. Hung TH, Liang CM, Hsu CN, Tai WC, Tsai KL, Ku MK, et al. Association between complicated liver cirrhosis and the risk of hepatocellular carcinoma in Taiwan. PLoS One. 2017;12:e0181858.
14. Tarek M, Louka ML, Khairy E, Ali-Labib R, Zakaria Zaky D, Montasser IF. Role of microRNA-7 and selenoprotein P in hepatocellular carcinoma. Tumor Biology. 2017;39:1010428317698372.
15. Rizk NI, Sallam AM, El-Ansary AR, El-Mesallamy HO. HMGB1 and SEPP1 as predictors of hepatocellular carcinoma in patients with viral C hepatitis: Effect of DAAs. Clin Biochem. 2019;70:8-13.
16. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164-71.
17. Burk RF, Early DS, Hill KE, Palmer IS, Boeglin ME. Plasma selenium in patients with cirrhosis. Hepatology. 1998;27:794-8.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/84923