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Correlations of Plasma Biotinidase Levels with Hepatic Synthetic Functions in Children with Chronic Liver Diseases

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Authors' contributions

This work was carried out in collaboration between all authors. Authors THS, HNE, AEA and NHA designed the study. Authors MHH, AAS and HME performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. All authors managed the analyses of the study, managed the literature searches and read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: Certain liver diseases can cause decreased synthesis of liver proteins or enzymes, including biotinidase, thereby reducing biotinidase activity in serum. The present study aimed to assess plasma biotinidase level in pediatric patients with compensated and decompensated chronic liver

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disease and to investigate the correlations between plasma biotinidase levels and the plasma albumin and prothrombin concentrations so that can identify the possible utility of plasma biotinidase levels as a predictor for hepatic synthetic function impairment .

Methodology: A total of 29 pediatric patients (20 male and 9 female) with chronic liver disease were included in the study (16 compensated and 13 decompensated). Plasma albumin, prothrombin time and concentration were measured in the included patients. Assay of plasma biotinidase level was done by ELISA, using commercially available assay kit, for both patients and control group.

Results: mean±SD of plasma biotinidase activities were found 4.4±1.2, 8.2±3, 8.7±0.7 IU\L (decompensated pediatric patients, compensated pediatric patients and control group respectively). Plasma biotinidase levels were statistically significant lower in pediatric patients with decompensated liver disease versus pediatric patients with compensated liver disease and control group ($p<0.001$). There was statistically significant negative correlation between plasma biotinidase levels versus prothrombin time "PT" and international normalization ratio "INR" ($p<0.05$) and statistically significant positive correlation between plasma biotinidase levels versus prothrombin concentration "PC" and albumin ($p<0.001$).

Conclusion: The findings of this study suggested that plasma biotinidase level could be used as a predictor for hepatic synthetic function impairment.

Keywords: Biotinidase; albumin; prothrombin; chronic liver disease; pediatric patients.

1. INTRODUCTION

Biotinidase, the biotin recycling enzyme is ubiquitously distributed and occurs at high levels in the liver, serum, and kidney. It is synthesized by the liver and secreted into the blood. The primary function of this enzyme is to cleave biotin from biocytin, thereby conserving biotin for use as a cofactor for four biotin-dependent carboxylases: propionyl CoA carboxylase (PCC), β-methylcrotonyl CoA carboxylase (MCC), pyruvate carboxylase (PC), and acetyl CoA carboxylase (ACC) [1]. The carboxylases play important roles in intermediary metabolism and their impairment can cause abnormalities in fatty acid synthesis, amino acid catabolism, and gluconeogenesis, resulting in the accumulation of abnormal organic acids. The absence or deficiency of biotinidase impairs the recycling of free biotin, thereby slowing the functioning of the biotin-dependent carboxylases [2].

A wide spectrum of clinical manifestations belongs to biotin deficiency; Including abnormalities of the neurological, dermatological, immunological, and ophthalmological systems has been reported [3].

As biotinidase is synthesized in the liver [4], certain liver diseases can cause decreased synthesis of liver proteins or enzymes, including biotinidase, thereby reducing its activity in serum [5].

Few studies could be traced in literature regarding the evaluation of plasma biotinidase in pediatric patients with chronic liver diseases as most studies has been done on adult patients, so the present study investigate the possibility of using plasma biotinidase as a marker for hepatic synthetic function and correlate it with plasma albumin, prothrombin time, concentration and international normalization ratio (INR) in children with chronic liver disease.

2. SUBJECTS AND METHODS

2.1 Study Population

This study included 29 pediatric patients from both sexes with chronic liver disease (16 compensated and 13 decompensated). All patients were selected from the department of pediatrics of Assiut, Sohag and Qena university hospitals. Consents were obtained from the all participate. Approval was taken from the university hospital ethical committee. The total duration of the study was thirty months (from July 1st 2011 up to December 31st 2013).

2.2 Laboratory Workup

1. Plasma collection and storage: 2 cc venous blood were drawn on EDTA for assay of biotinidase, they were then centrifuged at 3500 rpm for 15 min at 4℃ and the plasma were transferred into 1 ml cryotubes, and stored at -80℃ for later analyses.
2. Plasma albumin was estimated using [Cobas C311 (Roche diagnostics, Germany)], while, prothrombin time and concentration were measured using (BFT-II analyzer, Germany) immediately in the included patients.
3. Measurement of plasma biotinidase using an enzyme-linked immune-sorbent assay

(ELISA) kit supplied by (Glory Science Co., Ltd, CATALOG #: 95562, USA). The assay was done by ELISA multiskan EX microplate photometer, thermo scientific, STAT FAX-2100, USA] according to manufacturer protocol, in the included patients.

2.3 Statistical Analysis

Data were expressed as mean ± standard deviation, and range. For quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric test corresponding to student t-test for variables. Comparison between groups was done using non-parametric ANOVA test). *P* Values were two-tailed and were considered significant if < 0.05. Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12).

3. RESULTS

Regarding the demographic data of the studied groups: 29 pediatric patients (20 male and 9 female) with chronic liver disease (16 compensated and 13 decompensated) were involved in the present study with their mean age 3.3 ± 3.2 SD years, range 0.08-13 years. Regarding the etiological classification of chronic liver disease of the included pediatric patients, 7 patients had non-metabolic chronic liver disease (3 had secondary biliary cirrhosis, 1 autoimmune hepatitis, 3 had neonatal hepatitis with positive TORCH [toxoplasmosis, rubella, cytomegalovirus, herpes simplex]) and 22 patients had metabolic liver disease (5 patients had Wilson's disease, 2 patients had galactosemia, 2 patients had Gaucher disease, 2 patients had Niemann-Pick disease, 1 patient had mucopolysaccharidosis type-I "Hurler syndrome", 1 patient had tyrosinemia type-I while the remaining 9 patients had unclassified metabolic disorder) (Table 1).

The included patients have been subdivided into two categories: Those with compensated liver disease (n=16) and those with decompensated liver disease (n=13) based on the presence of proper liver synthetic functions in the form of normal albumin levels and prothrombin time and concentration, or not.

Table 1. Relative frequency of different etiologies of chronic liver disease of the included pediatric patients

Etiology of chronic liver disease of the included patients	No. (%)
Secondary biliary cirrhosis.	3 (10.3%)
Autoimmune hepatitis.	1(3.4%)
Neonatal hepatitis with positive TORCH.	3(10.3%)
Wilson's disease.	5 (17.2%)
Galactosemia.	2(7%)
Gaucher's disease.	2(7%)
Niemann-Pick disease.	1(3.4%)
Mucopolysaccharidosis type-I "Hurler syndrome".	1(3.4%)
Tyrosinemia type-I.	1(3.4%)
Unclassified metabolic disorder.	9(31%)
Total.	29 (100)

The mean ± SD of plasma biotinidase and different parameters of hepatic synthetic functions in patients with compensated versus patients with decompensated liver disease were presented in (Table 2) which revealed significant lower plasma biotinidase levels in pediatric patients with decompensated liver disease versus pediatric patients with compensated liver disease ($p<0.001$).

Table 2. Mean ± SD of plasma biotinidase and different parameters of hepatic synthetic functions in patients with compensated versus patients with decompensated liver disease

Parameters of hepatic synthetic functions	Pediatric patients with compensated liver disease n=16	Pediatric patients with decompensated liver disease n=13	P-value
PT (seconds) (Mean ± SD)	13.5±2	25±3.6	<0.05*
PC (%) (Mean ± SD)	89±30	49±23	<0.001**
INR (Mean ± SD)	1.1±0.4	2.5±1.2	<0.05*
Plasma Biotinidase (IU/L) (Mean ± SD)	8.2±3	4.4±1.2	<0.001**
Albumin (gm/ dl) (Mean ± SD)	4±0.6	2.3±0.3	$<0.05^{NS}$

PT: Prothrombin time; PC: prothrombin concentration; INR: international normalization ratio.

*NS P value >0.05 Non-significant, * P<0.05 significant, **P<0.001 highly significant*

The correlations between the plasma biotinidase and albumin, prothrombin time (PT), prothrombin concentration (PC), international normalization ratio (INR) in the patient group has been demonstrated in Figs. 1- 4.

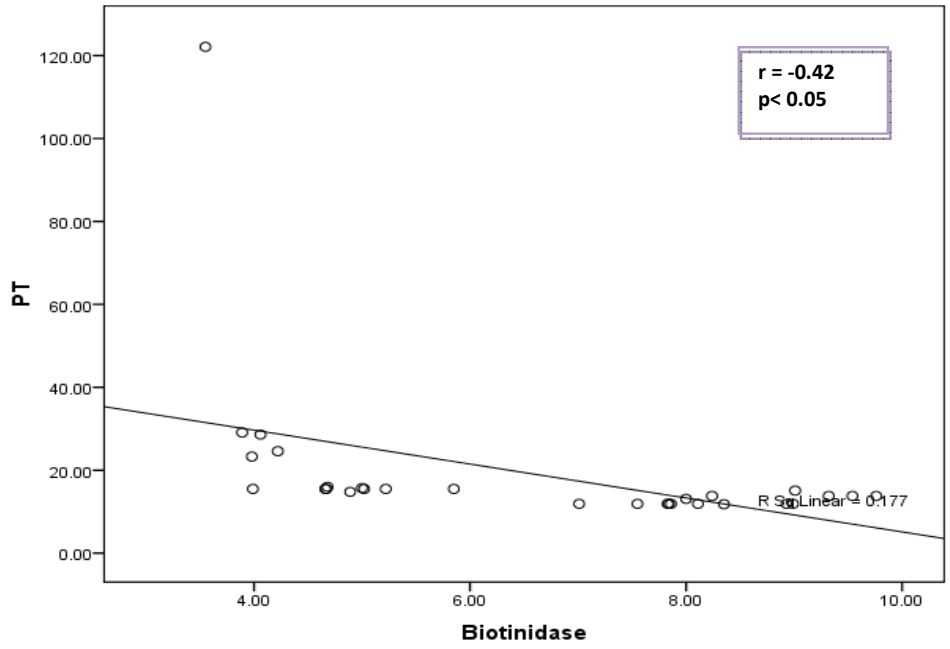

Fig. 1. Negative correlation between plasma biotinidase versus prothrombin time (PT) in the patients group

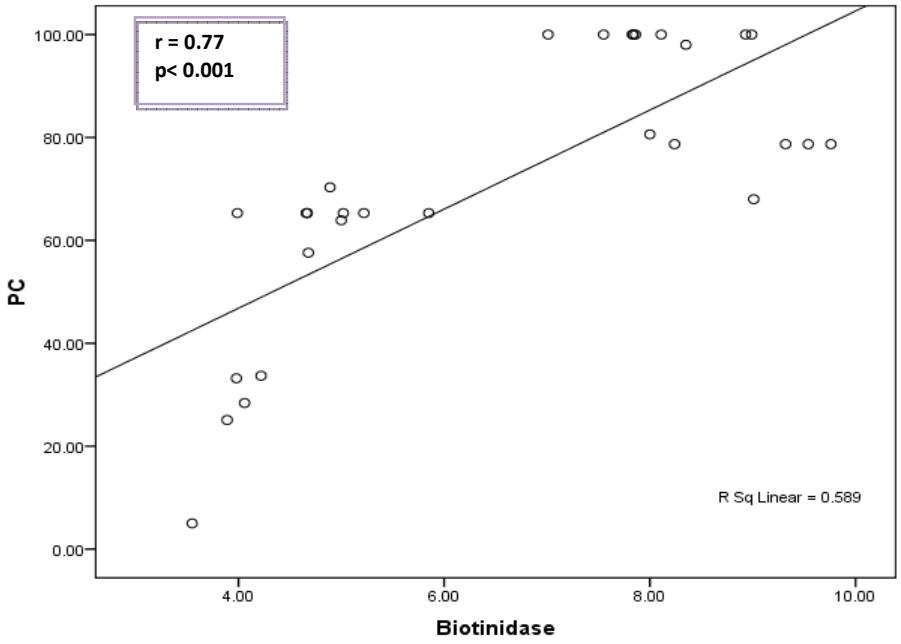

Fig. 2. Positive correlation between plasma biotinidase (IU/L) versus prothrombin concentration (PC) (%)

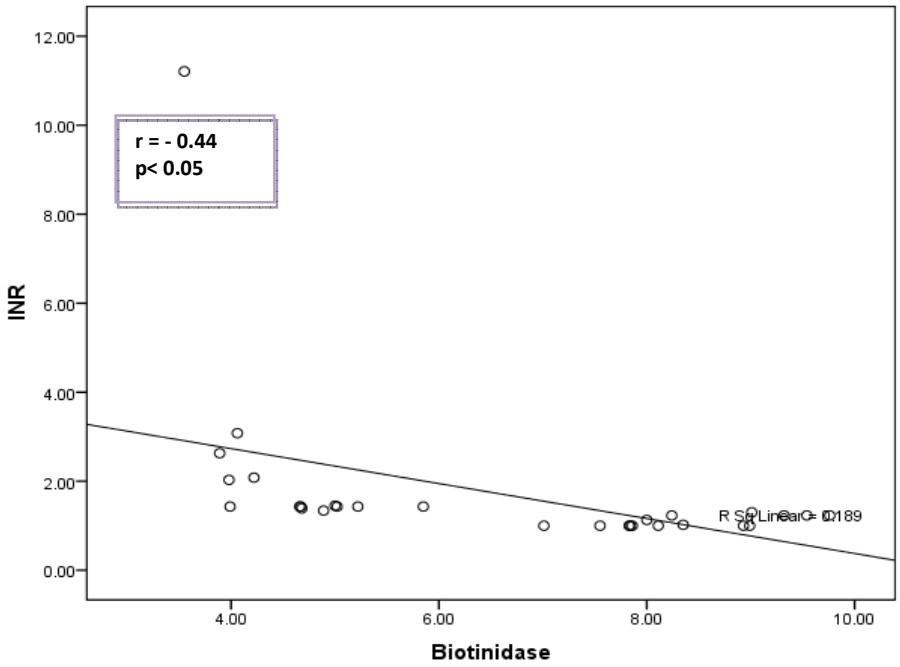

Fig. 3. Negative correlation between plasma biotinidase (IU/L) versus international normalization ratio (INR)

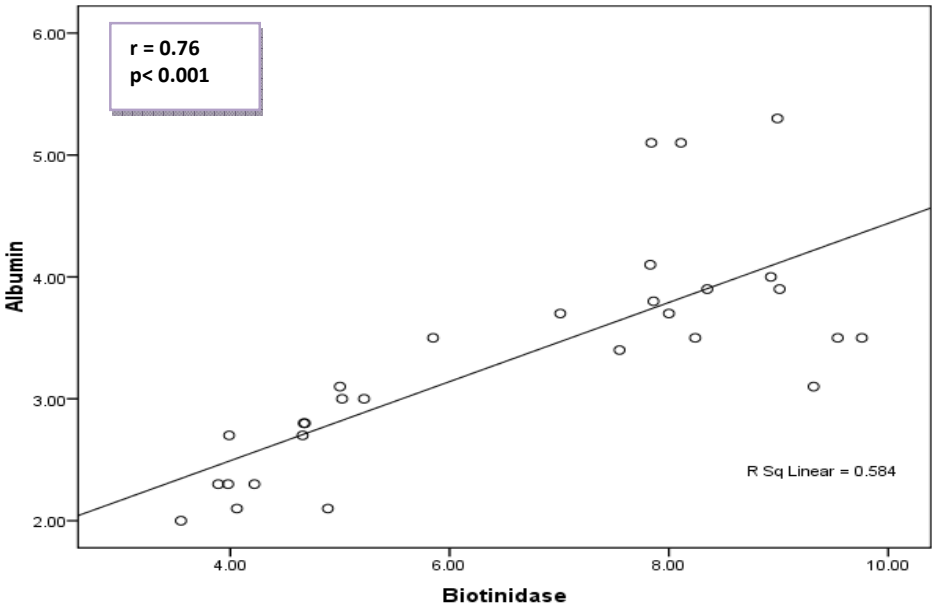

Fig. 4. Positive correlation between plasma biotinidase (IU/L) versus plasma albumin (gm/dl).

4. DISCUSSION

Biotinidase , the biotin recycling enzyme belongs to the nitrilase superfamily of enzymes that consists of amidases, N-acyltransferases and nitrilases [6]. Some members of the nitrilase superfamily (vanins-1, -2 and -3) share significant sequence similarities with biotinidase [7]. Biotin deficiency in humans is rare because biotin is continuously being recycled from the biotin dependent holocarboxylases by the action of biotinidase. Under normal conditions these

enzymes undergo proteolytic degradation to biocytin or biotinyl peptides. Cleavage of these breakdown products by biotinidase recaptures and recycles the free biotin for continued cofactor functioning. Biotinidase is also important for making biotin bioavailable from bound dietary sources [8]. Liver injury may influence biotinidase activity because it is mainly synthesized by the liver [9].

In this study, the total cases were classified according to the presence or absence of impaired prothrombin time "PT", prothrombin concentration "PC" and international normalization ratio "INR " and low plasma albumin into two subgroups, pediatric patients with decompensated liver disease (mean ±SD of PT, PC, INR & plasma albumin were 25±3.6, 49±23,2.5±1.2 & 2.3±0.3 respectively) & pediatric patients with compensated liver disease (mean ±SD of PT, PC, INR & plasma albumin were 13.5±2, 89±30,1.1±0.4 &4±0.6 respectively) . The plasma biotinidase showed highly statistically significant lower levels in pediatric patients with decompensated liver disease (4.4± 1.2) versus pediatric patients with compensated liver disease (8.2±3) with a p-value <0.001 .This is in agreement with a study that was done by Özdemir et al. [9] to assess serum biotinidase activity in adult patients with liver cirrhosis and to investigate the relationship between serum biotinidase activity levels and the degree of compensation of liver cirrhosis, concluding that serum biotinidase activity was significantly lower in patients with decompensated cirrhosis.

Also, the findings of this study is in agreement with a study done by Pabuçcuoğlu et al. [10] and a study done by Nagamine et al. [11] who concluded that serum biotinidase activity was significantly lower in patients with cirrhosis, particularly in the patients with decompensated cirrhosis and fulminant hepatitis that was associated with severe impairment of hepatocellular function.

This study clarified that there was statistically significant positive correlation between the plasma biotinidase level and PC and plasma albumin (p-value <0.001), the lower PC and plasma albumin the lower plasma biotinidase level. There was also statistically significant inverse correlation between the plasma biotinidase level and PT and INR with p-value <0.05, the higher PT & INR the lower plasma biotinidase level. These results were in agreement with a study done by Nagamine et al. [12] and Grier et al. [13], they correlate serum biotinidase activities with serum albumin and prothrombin time suggesting that biotinidase activities indicating the degree of liver damage, biotinidase activities were significantly reduced than in healthy controls.

5. CONCLUSIONS

The previous findings in this study indicate that the plasma biotinidase level is significantly decreased in patients with decompensated liver disease and so can be used as a predictor for hepatic synthetic function impairment. A larger scale studies are recommended to confirm the findings of the present study and to evaluate plasma biotinidase in various chronic liver diseases and correlate its level with the clinical staging of cirrhotic patients.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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