

Assessment of Serum Prolactin Levels in Patients with Liver Disease: A Cross-sectional Study

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ABSTRACT

Introduction: Prolactin is a hormone released from the anterior pituitary gland under tonic inhibitory control by dopamine. A decrease in dopamine levels is usually observed in decompensated liver disease, which could be due to its inhibition by the increased synthesis of false neurotransmitters. However, the level of serum prolactin in liver disease patients still remains disputed.

Aim: To evaluate the serum prolactin levels in patients with liver disease of different aetiologies and compare them with healthy controls.

Materials and Methods: The present cross-sectional study was conducted in the Department of Biochemistry from August 2021 to August 2022 at Amrita Institute of Medical Sciences (AIMS), Kochi, Kerala, India. A total of 100 patients with liver disease and 100 age- and gender-matched healthy controls were enrolled in the study. Serum prolactin was estimated using the Electro-Chemiluminescence Immuno Assay (ECLIA) technique. The serum

prolactin levels were compared among patients with liver disease of different aetiologies and with healthy controls. Statistical analysis was carried out using the Mann-Whitney U test, Kruskal-Wallis test, and Dun Bonferroni test.

Results: The median serum prolactin levels were significantly elevated in the cases {40.61 (29.13-70.24 ng/mL)} compared to the controls {17 (10.95-20.70 ng/mL)}. This p-value is correct as the median levels for cases is {40.61 (29.13-70.24 ng/mL)}. Comparison of prolactin levels showed no statistically significant difference based on the distribution of age and gender. In the present study, prolactin levels were found to be most prominent in patients with fatty liver disease.

Conclusion: The serum prolactin level increased significantly in liver disease patients, particularly in patients with fatty liver. Hence, prolactin levels can be used as a useful predictive biomarker for fatty liver.

Keywords: Biomarker, Dopamine, Fatty liver, Neurotransmitter

INTRODUCTION

According to the World Health Organisation, liver disease is the tenth most common cause of death in India. Approximately 2 million deaths per year are reported due to liver disease, making it a major cause of mortality and morbidity worldwide [1]. Liver diseases are often associated with hormonal changes, which can be reversible with the recovery of liver function [2,3]. Deteriorated liver function can result in the incorrect entry of amino acids into the central nervous system, leading to the production of false neurotransmitters that may inhibit the release of dopamine. Since dopamine exerts negative control over prolactin, it can cause hyperprolactinemia. Some studies have shown prolactin to be an indirect prognostic marker for liver diseases [4,5], as high prolactin levels can be associated with increased liver complications.

Prolactin (PRL) is a polypeptide hormone regulated by hypothalamic factors such as Prolactin Releasing Factors (PRFs) and Prolactin Inhibitory Factors (PIFs). Recent reports suggest that pituitary prolactin secretion is suppressed by the neurotransmitter dopamine. An evidence-based study reported that alterations in dopamine levels are observed in liver diseases, but it cannot be measured in any body fluids or the brain [6-10]. Given the increasing prevalence of liver diseases, prolactin can serve as a biomarker to assess disease severity, complications, and as a tool for early intervention.

Many researchers have studied the association of serum prolactin levels in liver cirrhosis, an advanced level of liver disease [11-13]. However, few studies have assessed the serum prolactin levels in liver diseases of various etiologies [14-16]. Additionally, there is a paucity of data regarding the association of serum prolactin levels in various liver diseases in the South Indian population [17,18].

Therefore, this study was conducted to investigate alterations in serum prolactin levels in liver diseases of different aetiologies and to compare these levels with controls in a tertiary care centre in Kochi, Kerala.

MATERIALS AND METHODS

The present cross-sectional study was conducted on subjects who attended the Gastroenterology Outpatient Department (OPD) and samples were analysed in the Department of Biochemistry at Amrita Institute of Medical Sciences (AIMS), Kochi, Kerala, India. from August 2021 to August 2022. The study received approval from the Institutional Ethics Committee, AIMS (ECASM-AIMS-2022-089; dated 22/04/2022). Written informed consent was obtained from all study participants after explaining the purpose of the study.

Inclusion criteria: The study included subjects aged between 15 and 50 years who were known cases of liver disease, with or without complications, as the cases. Age- and gender-matched subjects without liver diseases were enrolled as controls.

Exclusion criteria: Pregnant and breastfeeding women, patients with persistent and chronic renal failure, hypothyroid patients, patients on drugs such as thioxanthene, oestrogen, anti-androgen, and those with previous documentation of pituitary tumours were excluded from the study.

Sample size calculation: The minimum sample size, including both the case and control groups, was calculated to be a total of 200 based on the mean serum prolactin levels in patients with liver disease (44.00±28.92 ng/mL). and healthy adults (11.22±3.54 ng/mL) observed in a previous study by Giri R et al., with 80% power and 95% confidence [19].

Data collection: Age and gender data were collected from all study participants. A 2 mL random blood sample was collected from each subject. Serum prolactin levels were assayed using the sandwich principle of electrochemiluminescence immunoassay with a total duration of 18 minutes, and it was estimated on a Roche Cobas 8000 I series auto-analyser. The serum prolactin levels were compared among patients with liver disease of different aetiologies and with healthy controls.

Reference range of serum prolactin [20,21]:

Males: 4.6-21.4 ng/mL

Females: 6.0-29.9 ng/mL

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM Statistical Packages for Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, USA). Descriptive statistics for both groups were expressed as mean±Standard Deviation (SD) for continuous variables and frequency and percentage for categorical variables. To assess the statistical significance of the differences in mean or median values among groups for numerical variables, the Kruskal-Wallis test was applied. Multiple comparison tests were conducted using the Dun Bonferroni test. A p-value <0.05 was considered statistically significant.

RESULTS

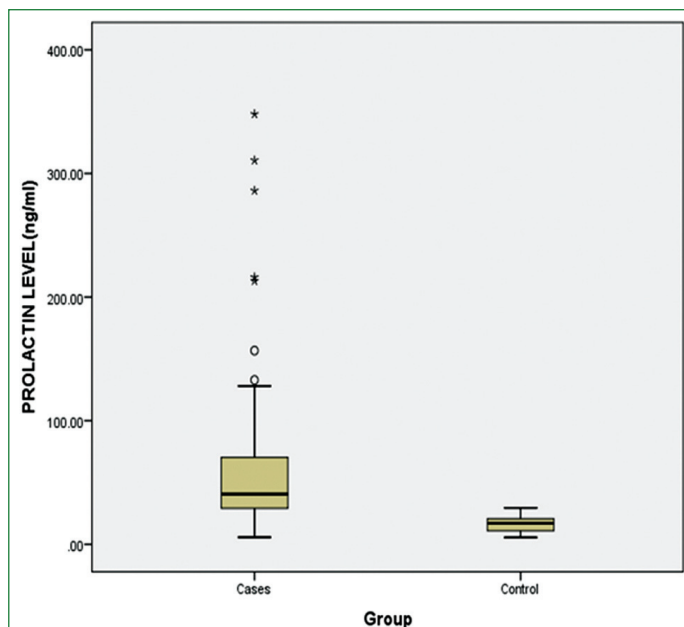
The study included a total of 116 males and 84 females with a mean age of 32.72±38.05 and 44.96±56.21 respectively. In the present study, out of the total 200 participants, 58% were males and 42% were females. According to the age-wise distribution, in the case group, 26% and in the control group, 27% were in the age group of 15-27 years. For the age group of 28-35 years, there were 25% cases and 22% controls. In the age group of 36-43 years, there were 24% cases and 29% controls, and in the age group of 44-50 years, there were 25% cases and 22% controls [Table/Fig-1].

Parameters	Cases (n=100)	Controls (n=100)	Total (N=200)	p-value
Age (years)				
15-27	26	27	53	0.549
28-35	25	22	47	
36-43	24	29	53	
44-50	25	22	47	
Gender				
Male	62	54	116	0.112
Female	38	46	84	

[Table/Fig-1]: Distribution of subjects according to age and gender.

The mean value of prolactin level was 59.28±58.61 (29.13-70.24 ng/mL) in cases and 16.44±6.53 (10.95-20.70 mg/mL) in controls, and this difference was found to be statistically significant with a p-value <0.001 [Table/Fig-2]. The maximum level of prolactin was seen in women with fatty liver disease (161.08±93.85), and the lowest level was found in male Non Alcoholic Steatohepatitis (NASH) with a mean value of 10.56±3.04. The comparison of mean prolactin levels of various liver diseases was found to be statistically significant (p <0.001) [Table/Fig-3].

In present study, the maximum level of prolactin was seen in fatty liver disease patients (148.20±90.29 ng/mL), followed by hepatitis (61.46±25.32ng/mL), and the lowest levels were found in Non Alcoholic Steatohepatitis (NASH) with a mean value of 15.35±11.09 ng/mL) The comparison of median prolactin levels of various liver diseases was found to be statistically significant (p<0.001) [Table/Fig-4].



[Table/Fig-2]: Box-whisker plot showing prolactin levels between study groups.

Liver diseases	Males		Females		p-value
	n (%)	Prolactin level (ng/mL) (Mean±SD)	n (%)	Prolactin level (ng/mL) (Mean±SD)	
Acute liver failure	4 (6.5%)	32.01±5.84	6 (15.8%)	39.24±7.66	<0.001
Alcoholic liver disease	12 (19.4%)	46.39±34.89	0	0	
Chronic liver disease	11 (17.7%)	37.67±10.66	0	0	
Fatty liver	2 (3.2%)	83.8±21.07	10 (26.3%)	161.08±93.85	
Hepatic encephalopathy	8 (12.9%)	63.65±17.83	7 (18.4%)	48.58±9.19	
Hepatitis	1 (1.6%)	39.18	9 (23.7%)	63.94±25.53	
Liver cirrhosis	17 (27.4%)	63.18±77.79	3 (7.9%)	41.38±9.07	
NASH	7 (11.3%)	10.56±3.04	3 (7.9%)	26.52±16.06	

[Table/Fig-3]: Distribution of patients with liver diseases according to gender.

Liver diseases	n (Frequency)	Mean±SD	Median (Q1-Q3)	p-value
Acute liver failure	10	36.35±7.61	36.00 (32.01-39.40)	<0.001
Alcoholic liver disease	12	46.39±34.89	29.68 (22.90-61.57)	
Chronic liver disease	11	37.67±10.66	38.65 (29.52-42.67)	
Fatty liver	12	148.20±90.29	120.50 (89.10-186.35)	
Hepatic encephalopathy	15	56.62±15.99	51.82 (45.09-70.24)	
Hepatitis	10	61.46±25.32	60.65 (39.18-85.40)	
Liver cirrhosis	20	59.91±71.89	38.09 (27.59-67.55)	
NASH	10	15.35±11.09	11.78 (10.58-16.29)	

[Table/Fig-4]: Comparisons of prolactin levels in patients with various liver diseases.

DISCUSSION

Liver disease is a broad term that encompasses various conditions leading to liver dysfunction and the impairment of its functions. It has been observed that impaired liver function can inhibit dopamine release in the central nervous system, which may result in hyperprolactinemia due to reduced dopamine release from the hypothalamus [5]. Therefore, studying whether prolactin can serve as an indirect biomarker to predict the severity and complications of liver disease holds potential advantages. The present study aimed to assess serum prolactin levels in patients with liver disease compared to healthy controls. The study did not find a statistically

significant relationship between prolactin levels in patients and age or gender distribution. This finding is consistent with a study conducted by Morgan MY et al., which also reported no correlation between prolactin levels and patient gender [5].

The median serum level of prolactin in cases was found to be 40.61 (29.13-70.24), which differed significantly when compared to that in controls, 17 (10.95-20.70), with a p-value <0.001. Based on the study results, liver cirrhosis was observed to be the most prevalent liver disease, with a prevalence of 27.4% in males and 7.9% in females. Overall, liver disease was found to be more prevalent in men (n=62) than in women (n=38); however, the prevalence of fatty liver and hepatitis was higher in women. A study conducted by Rajasekarapandian TK and Kanimozhi J reported that male cirrhotic patients had serum prolactin levels 11.38 times higher than female cirrhotic patients [1].

Similar findings were observed in the study by Zhang P et al., which showed a positive correlation between prolactin levels and the severity of Non Alcoholic Fatty Liver Disease (NAFLD) [22]. Consistent with present study, among the group of fatty liver patients, women had higher levels of serum prolactin. This could be attributed to increased oestrogen levels in fatty liver, which stimulate prolactin release through interference with dopamine from the hypothalamus and direct effects on the anterior pituitary.

A significant correlation was also observed between serum prolactin levels and hepatic encephalopathy patients. A study by Giri R et al., also concluded that serum prolactin can be exercised as an indicator of the severity of hepatic encephalopathy, suggesting that patients with higher serum prolactin levels in hepatic encephalopathy require urgent and intensive medical care [19]. With the increasing prevalence of liver diseases, the use of inexpensive and non invasive markers like prolactin can help indicate the severity of the disease and its complications, serving as a tool for early intervention.

A comparison of the findings in the present study with previous studies is shown in [Table/Fig-5] [1,5,13,19,22].

Author's name	Place and year of the study	Sample size/ type of study	Findings	Present study findings
Morgan MY et al., [5]	London 1978	150 patients	No relationship existed between the prolactin value and the gender of the patient, the aetiology of the liver disease, the severity of the liver disease.	Age and gender were not statistically significant (p-value 0.549 and 0.112, respectively). Among the group of fatty liver patients, women were found to have higher levels of serum prolactin. This could be due to the increased oestrogen levels seen in fatty liver.
Rajasekarapandian TK and Kanimozhi J [1]	Tamil Nadu 2019	100 patients	Male cirrhotic patients have elevated serum prolactin level 11.38 times more than female cirrhotic patients.	Based on the study results, liver cirrhosis as the most prevalent liver disease (males=17 (27.4%) and females=3 (7.9%)).
Giri R et al., [19]	India 2021	70 patients	Hepatic encephalopathy patients with higher serum prolactin levels need urgent and intensive medical care.	This study observed that a significant association existed between serum prolactin level and hepatic diseases.
Zhang P et al., [22]	Japan 2019	873 patients	There was a positive correlation between prolactin level and the severity of NAFLD.	A significant association was found between prolactin level and the severity of NAFLD.

Khalil MF et al., [13]	Egypt 2017	50 patients	PRL level increases significantly with severity of liver disease particularly in patients with hepatic encephalopathy. High PRL level could therefore be considered as a negative prognostic marker of liver cirrhosis.	This study observed that a significant association existed between serum prolactin level and hepatic diseases.
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[Table/Fig-5]: Comparison of previous studies with the present study [1,5,13,19,22].

Limitation(s)

The limitations of present study were its single-centre design and short duration. A detailed study involving a larger, multicentre population is warranted.

CONCLUSION(S)

Based on the results of present study, it was observed that liver cirrhosis is the most prevalent liver disease in males compared to females. Prolactin levels increase significantly in liver diseases, especially in patients with fatty liver and hepatic encephalopathy. High prolactin levels could therefore be considered a prospective biomarker for fatty liver, mainly in women. Serum prolactin also has the additional advantage of being a relatively inexpensive and non invasive marker for diagnosing fatty liver. Research needs to be done to determine whether there is any relationship between the severity of fatty liver and prolactin levels. Further studies are also required to investigate whether prolactin levels correlate with the treatment of fatty liver and hepatic encephalopathy. Hence, more research is needed to fully explore the potential of serum prolactin as a non invasive biomarker for fatty liver disease.

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