ORIGINAL ARTICLE

RELATIONSHIP BETWEEN HYPOGONADISM AND SERUM TESTOSTERONE LEVELS IN CHRONIC LIVER DISEASE

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Background: Men with extensive chronic liver disease usually have low levels of testosterone in the serum. This study looked at the relationship between hypogonadism and low serum testosterone levels in patients with chronic liver disease. **Methods:** This retrospective study was conducted at Central Park Teaching Hospital, Lahore from Jan 2022 to Jan 2024, on patients between 5 to 60 years of age. After approval from ERB and permission from the authorities, records were retrieved. Two hundred records of men with hepatic cirrhosis and verified hypogonadism were divided into alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), while records of 150 men as control group were include in the study. Patients' data for 'Sex Hormone Binding Globulin (SHBG)' and 'total testosterone' were collected and entered into MS Excel file. Using SPSS-22 independent Student's *t*-test was applied for statistical analysis. **Results:** No statistically significant variations were observed (p=0.101) in the means of SHBG across two groups but there was a statistically significant (p<0.05) variation in blood serum testosterone levels between age groups. **Conclusion:** Hypogonadism and low levels of testosterone are strongly linked to male patients with cirrhotic liver conditions, particularly in those with ALD, while no significant impact of SHBG was found between the two groups. Significant differences were observed between patients with ALD and NAFLD in terms of testosterone levels.

Keywords: Hypogonadism, Testosterone, Sex hormone binding globulin, chronic liver disease

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INTRODUCTION

Chronic liver disease (CLD) is a chronic disease that affects the normal functioning of the liver more than any other disease worldwide. It includes different ailments such cirrhosis as well alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH) and is female-dominated.[1] All these conditions are associated with acute and chronic systemic complications. One of the most important is the endocrine disruption which is often present in CLD and so-called males of Hypogonadism.[2] One of the common endocrinological disorders seen in male distinct cases of chronic liver disease is known as hypogonadism. It appears in the imbalance of the gonadal function with the decrease in testosterone gained and sexual reproductive capacities.[3] The association of testosterone levels and hypogonadism among CLD patients is a topic of pressing concern for clinicians, as this relationship could have a bearing on the patient's well-being and the potential course of the disease.

Often in males who have advanced chronic liver disease, the organ's ability to orchestrate metabolic processes concerning hormones is diminished.[4] This impairment may cause the patient's serum testosterone levels to be severely depressed, which in practice, is detrimental to the clinical condition of such patients. Most testosterone is produced in the testes and is important for men in terms of muscle mass, bone density, sexual drive, and general activity. Plasma testosterone is inactivated in the liver enzymes and any injury to the liver will interfere with the availability of the hormone thereby causing certain endocrine abnormalities such as hypogonadism. Such SHBG, produced by the liver, also controls the amount of circulating testosterone that can exert actions in various tissues. Hypothetically, any marked derangement of liver function would ultimately result in further derangements of the SHBG and tobacco concentrations which will, in most cases, lead to a decrease in the concentrations of free active testosterone.[5,6]

This study seeks out the linkage between hypogonadism and serum testosterone levels in patients with chronic liver disease.[7,8] The particular assessment intends to understand how testosterone levels differ among patients with two forms of liver disease, NAFLD and ALD, and the implications of these diseases on endocrine activity.[9] This research aims to expand knowledge regarding hormonal dysfunction in terms of total testosterone and SHBG levels, particularly hypogonadism, in liver disease, and provide a new understanding of the potential reasons for this condition in cirrhotic patients.

METHODOLOGY

This cross-sectional study was approved by the Institutional Ethical and Review Board of Central Park Medical College Lahore vide CPMC/IRB-NO/1412. From 1 Jan 2022, to 30 Jan 2024, this study was

conducted at the Medicine OPD of Central Park Teaching Hospital, Lahore. In this investigation, male patients aged 15–60 years were enrolled. The study procedure was authorized by the Institutional Review Board. Participants with additional metabolic or systemic problems like diabetes mellitus and autoimmune diseases were excluded. Hypogonadism was defined as a total serum testosterone level in the early morning hours that is <300 ng/dL. We verified that the blood specimens for testosterone and were taken in the early hours of the morning. The means for each variable across all age groups were compared using independent Student's *t*-test, and $p<0.05$ was considered statistically significant.

RESULTS

There were significant differences in age, BMI, and testosterone levels between patients with Alcoholic Liver Disease (ALD) and those with Non-Alcoholic Fatty Liver Disease (NAFLD). The mean age of patients with ALD was significantly higher, at 47.2±0.3 years, compared to 24.4±0.5 years for NAFLD patients ($p<0.001$). Patients with ALD had substantially lower serum testosterone levels, with a mean of 4.4±0.1 ng/dL, compared to 8.2±0.4 ng/dL in NAFLD patients, showing a significant difference ($p<0.001$). (Table-1).

The mean levels of Sex Hormone-Binding Globulin (SHBG) were slightly lower in ALD patients (15.0±0.5 nmol/L) compared to NAFLD patients, but this difference was not statistically significant (p=0.101). The testosterone levels showed significant differences between ALD and NAFLD patients, while SHBG did not vary significantly.

Table-1: Comparison of Testosterone and SHBG in patients with ALD and NAFLD

Parameters	Groups	Mean	SEM	*p*
Testesterone (ng/dL)	ALD	4.4	0.1	<0.001
	NAFLD	8.2	0.4	
SHBG (nmol/L)	ALD	15.0	0.5	0.101
	NAFLD	19.1	2.4	

Independent sample *t*-test was applied, $p\leq0.05$=Significant

DISCUSSION

Our research revealed a statistically significant difference in blood testosterone levels between the two age groups of ALD and NAFLD when the levels were stratified. ALD patients had a significantly low level of total testosterone. The patient with hypogonadism resulting from liver cirrhosis had the lowest blood testosterone level. There are several possible explanations for the documented connection between low testosterone levels and NAFLD in men. For instance, low serum testosterone levels lead to deposition of visceral adipose tissue, which can exacerbate insulin resistance and raise the amount of free fatty acids the liver is exposed to. There is a correlation between increased inflammation and lower testosterone levels. Testosterone may also affect liver microRNAs or hepatic lipase activity, as seen in male rats.[10] Since enzymes such as 5-reductase and aromatase may convert testosterone to Dihydrotestosterone (DHT) and E2, the DHT and E2 may have a role in the link between low serum testosterone levels and NAFLD in males.[11] Reduced DHT levels may be a factor in NAFLD in male mice with hepatic steatosis due to a 5-reductase deficiency or inhibition.[12] Low levels of DHT may add to the pathogenesis of NAFLD and increase the risk of hepatocellular carcinoma, or HCC because DHT can cause an arrest of cell cycle and apoptosis in 'androgen sensitive' cells in the liver via the PKR/eIF2a signalling pathway.[13]

Males with lower testosterone also had higher E2 levels, which might be the consequence of a higher conversion of testosterone to E2. It has been found that E2 inhibits fatty acid synthase and acetyl coenzyme A phosphorylation, which in turn inhibits lipogenesis in male rats. Therefore, E2 could have an impact on the connection between testosterone and NAFLD.[14]

It is established that in individuals with liver cirrhosis, there is a positive correlation between the degree of liver disease elevated levels of plasma oestrogen, and decreased levels of plasma testosterone. It was demonstrated that cirrhosis patients' plasma levels of prolactin hormone and SHBG were noticeably elevated. One of the factors that lead to the development of hypogonadism in individuals with liver cirrhosis is the existence of portosystemic shunts.[15]

In this investigation, when patients with alcoholism or drug abuse-related liver cirrhosis were identified, low serum levels of testosterone did not influence SHBG. When testosterone is in the bloodstream, a minimum of two plasma proteins (albumin and SHBG) bind to it. It is generally accepted that unbound free testosterone is the substance that enters the cell and causes androgenic effects. While blood SHBG levels in liver cirrhosis are normal, it is important to remember that the overall testosterone level does not adequately reflect testosterone activity.[16] A study conducted on senior males using cross-sectional research found that an increase in total testosterone was linked to a 57% lower chance of being diagnosed with metabolic syndrome. Low SHBG and total testosterone levels are indicative of metabolic syndrome in a group of middle-aged male Finns. Although there is a strong correlation between androgen and metabolic syndrome, a causal link has not been shown.[17,18]

Overt feminization and hypogonadism are common clinical symptoms in males with chronic liver disease. Along with these features, cirrhotic males have been shown to have low plasma concentrations and reduced testosterone production, with only a small percentage of cirrhotic men appearing to have a little increase in circulating biologically active hormones (oestrogens).[19]

Although our study found no significant difference in SHBG levels between ALD and NAFLD patients, this might be due to the complex interactions of liver function with hormone-binding proteins. Previous research suggests that despite normal SHBG levels, testosterone bioavailability might be affected by altered liver function, impacting testosterone activity in cirrhotic patients. While some previous research revealed no change in testosterone concentration with age, others indicated an increase with age. Males largely get their testosterone via the peripheral aromatization of circulating testosterone, and the rate of aromatization is known to be influenced by obesity. One possible explanation for the lower blood testosterone levels in our participants might be that they were not fat, and the older subjects had a considerably lower BMI.[20]

CONCLUSION

Hypogonadism and low levels of testosterone are strongly linked to male patients with cirrhotic liver conditions, particularly in those with ALD, while no significant impact of SHBG was found between the two groups. Significant differences were observed between patients with ALD and NAFLD in terms of testosterone levels. Further research is needed to explore the underlying mechanisms and the potential clinical implications of testosterone in liver disease progression.

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K: Data collection
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