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ORIGINAL ARTICLE

Low Serum Testosterone Level and Its Relationship with Hypogonadism in Patients with Chronic Liver Disease

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ABSTRACT

Objective: Loss of libido, low serum testosterone levels, and other symptoms of hypogonadism like subfertility, gynecomastia, and immature testes, is a prevalent medical condition amongst males with advanced chronic liver disease. The purpose of this investigation was to evaluate the low serum testosterone levels association with hypogonadism in people with chronic liver disease.

Study Duration: This study was carried out at Outpatient Department (OPD) of Medicine Ayub Teaching Hospital, Abbottabad from 1st January 2022 to 30th June 2022.

Material and Methods: The retrospective study was completed on two hundred confirmed patients of hypogonadism with liver cirrhosis. In the repository, the available data was divided into two groups. The first group of chronic liver disease patients was diagnosed due to non-alcoholic fatty liver disease (NAFLD) and second patient group due to alcoholic liver disease (ALD). The patient in NAFLD group were in the age group between15-30 years whereas the patients from ALD group were 30-60 years of age. The diagnostic values of total testosterone and Sex hormone binding globulin (SHBG) were collected from patient's record. The independent t test was used for statistical analysis by using SPSS version 22. The frequency distribution of testosterone was also calculated between two types of chronic liver disease patients.

Results: The retrospective research was performed. The data were dispersed across two age groups. The youth had no alcohol-related data, while the elderly had. According to hospital data, distribution was based on age between 15 and 30 years (NAFLD) and between 30 and 60 years (ALD). When T-test was applied it showed that there was no statistically significant difference found in means of SHBG between two age groups amongst chronic liver disease patients. In the case of serum testosterone, there was a statistically significant (p 0.05) difference between agegroups (Table 1). Figures 1 and 2 illustrate the frequency distribution of total testosterone andits comparison within the liver cirrhosis group, respectively.

Practical Implication: Our study predicted that low testosterone can raise the risk of mortality, the necessity for liver transplantation, and the likelihood of severe infection in men with cirrhosis given the mechanisms of action of testosterone.

Conclusion: On the basis of two groups of liver cirrhosis, there is a significant age-related change in total serum testosterone, its control by the pituitary and it's binding to SHBG in males over the age of forty. However, no substantial data was discovered in sex hormone binding globulin. Low testosterone levels are associated with hypogonadism in patients with cirrhosis of the liver. The effect of testosterone replacement treatment on increasing muscle quality in male cirrhotic patients remains to be determined. Safety and effectiveness of the treatment requires additional prospective research.

Keywords: Sex Hormone Binding Globulin, Serum Testosterone, Hypogonadism, Chronic Liver Disease

INTRODUCTION

Although it is usually accepted that testosterone levels in men decline with ageing, it is still unclear mechanism with hypogonadism amongst liver cirrhosis patients. This is primarily due to unavailable and contradictory data regarding developmental changes in hormone release from gonads, their hypothalamic-pituitary regulation, and sex hormone binding globulin (SHBG) levels, which evaluate the releasing of free hormones in the exchange system.[1] During puberty, there is no doubt that serum androgen levels increase rapidly. However, there are still many controversies regarding the changes in gonadal hormones and their regulatory hormones in older men.[2] Some authors believe the age-related decline in gonadal function and serum concentration of sex hormones justifies andropause as the male equivalent of menopause. Some reports also indicate that the SHBG in the blood is altered. The accessibility of sexual hormones in the body is the result of these various factors. Aging is one of the factor related with the development of chronic systemic disorders. The concentration of gonadal hormones and how they are regulated can be affected by the increased drug exposure within the body.[3] In male patients with liver cirrhosis, hypogonadism drives the progress of the vast majority of proven symptoms and displays a rather broad range of findings. Hypogonadism is characterized by a number of symptoms and signs, including palmar erythema, spider angioma, telangiectasia, decreased and altered distribution of secondary sexual hair, gynecomastia, undersized testis, low libido, and impotence. Hypogonadism is connected with liver cirrhosis.[4] It was found that individuals with liver cirrhosis who had clinical signs such as gynecomastia, spider angioma and palmar erythema had greater serum estrogen levels than patients with liver cirrhosis who did not have these clinical signs. Abnormally low weight, starvation, and extreme exercise can contribute to reduced testosterone levels and poor fertility in underweight individuals.[5] Although the etiopathogenesis of osteoporosis in chronic liver illnesses is not completely understood, it may be a complex process. Investigations that were carried out in clinical settings on male patients who had alcoholic cirrhosis showed that there was a rise in the number of bone-destroying osteoclasts and a fall in the amount of bone being formed by osteoblasts and other bone-forming cells alongside a decrease in testosterone levels.[6]

To pinpoint the anatomic site and biochemical mechanism causing the reported men with a variety of alcoholic liver diseases had their hypothalamic-pituitary-gonadal activity assessed. Exogenous chorionic gonadotropin did not result in a 50% increase in plasma testosterone for more than one third of patients. This is

comparable to the previous finding. Therefore, primary gonadal failure and hypothalamic- pituitary suppression are present in individuals who have alcoholic liver disease.[7,8]

Hepatic steatosis is characterized by hepatic fat buildup and is regarded the precursor of non- alcoholic fatty liver disease (NAFLD). As NAFLD continues, liver inflammation and damagecan eventually result in cirrhosis, liver failure, and frequently hepatocellular cancer. Hepatic steatosis correlates linearly with the

incidence of metabolic syndrome (MetS), obesity, andthe defining characteristics of these disorders, including insulin resistance, hyperinsulinemia, and dyslipidemia.[9]

Consequently, the purpose of the study was to determine the levels of testosterone and SHBG in liver cirrhotic patients in the ages from 15 to 30 years in NAFLD group and 30 to 60 years in ALD group to compare the means of the variables being measured different liver cirrhotic patients. To the best of author's knowledge no such study is conducted in Pakistan before this so this will provide local confirmations about low serum testosterone level and its relationship with hypogonadism in patients with chronic liver disease.

SUBJECTS AND METHODS

A total blood testosterone level of less than 300 ng/dL in the early morning shows hypogonadism. This study was carried out at Outpatient Department (OPD) of Medicine Ayub Teaching Hospital, Abbottabad from 1st January 2022 to 30th June 2022. Male patients having age 15 to 60 years were included in this study. Each participant provided written informed consent for participation in this study. Ethical Committee approved the study procedure. The patients were all chronic liver disease males with diagnosed hypogonadism collected from hospital data. The data was comprehensive clinical and laboratory examination. There were only males selected for the study. Efforts were made to exclude participants with other metabolic or systematic disorders. We confirmed that the blood samples were drawn between 8 and 9 a.m.

The subjects were divided into two age groups: group 1 from ages 15 to 30 years (NAFLD), group 2 from ages 31-60 years (ALD). Using the independent t test, the means of all age groups for each variable were compared. The frequency distribution of testosterone levels in both groups of liver cirrhosis was calculated. Frequency was used for plotting the graphs.

RESULTS

The retrospective study was conducted. The data were divided into two age groups. The 15-30 age group had no alcoholic data, but it was found in 30-60 age groups. So, the patients were divided according to age between 15 and 30 years (NAFLD), while those aged 30-60 years were alcoholic patients (ALD). This was proven by hospital data. The independent t test revealed no statistically significant differences in the means of SHBG between age groups (p
> 0.05). The serum testosterone was significantly low (p<0.05) in ALD patients. The statistically significant mean difference was found in age, BMI and testosterone level (table 1). Figure 1 and 2 displays the frequency distribution of total testosterone altogether and compared within liver cirrhosis group, respectively.

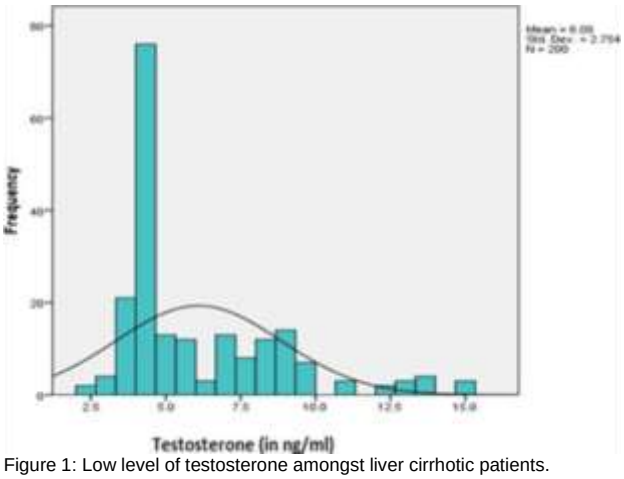

Figure 1: Low level of testosterone amongst liver cirrhotic patients.

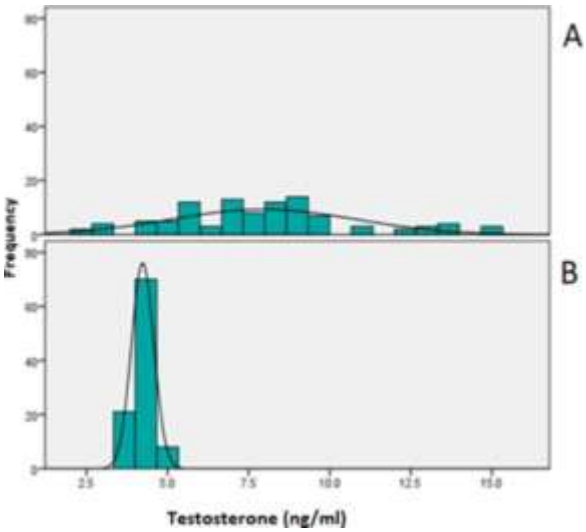

Figure 2: Comparison of frequency distribution of testosterone amongst liver cirrhoticpatients. A: Non-Alcoholic Fatty liver disease and B: Alcoholic Liver disease

Table 1: Baseline and clinical parameter difference between NAFLD and ALD

Baseline and Clinical Parameters		Mean	SEM	P-Value
Age in years	NAFLD	23.3	0.6	<0.001
	ALD	46.3	0.4	
BMI (kg/m2)	NAFLD	23.3	0.4	<0.001
	ALD	14.6	0.4	
Glucose level (mg/dl)	NAFLD	78.1	0.8	0.591
	ALD	78.7	0.9	
Testosterone (ng/ml)	NAFLD	8.0	0.3	<0.001
	ALD	4.2	0.0	
SHBG (nmol/L)	NAFLD	18.5	2.1	0.101
	ALD	14.9	0.3	

The independent sample t test was used the level of significance (p<0.05).

DISCUSSION

Our study found that when serum testosterone level was stratified with two age groups of NAFLD and ALD a statistically significant difference was found. Similarly, the significant low level of total testosterone and underweight BMI were found in ALD patients. In figure 2, the lowest serum testosterone level was found in the hypogonadism patient due to liver cirrhosis. Several distinct processes may account for the reported relationship between low testosterone and NAFLD in males. For example, decreased testosterone levels result in the buildup of visceral adipose tissue (VAT), which can contribute to insulin resistanceand an increase in the liver's exposure to free fatty acids. In addition, reduced testosterone levels are related with higher inflammation. As shown in male rats, testosterone may also impact microRNAs in the liver or the activity of hepatic lipase.[10] Since testosterone can be transformed to Dihydro testosterone (DHT) and E2 by the enzymes 5-reductase and aromatase, DHT and E2 may contribute to the association between low testosterone and NAFLD in males.[11] Male mice with a deficit or inhibition of 5-reductase exhibit hepatic steatosis indicating that decreased DHT levels may contribute to NAFLD.[12] As DHT can induce cell cycle arrest and death in androgen-sensitive liver cells via the PKR/eIF2a signaling pathway low levels of DHT may raise the risk of hepatocellular carcinoma (HCC) and play a role in the pathophysiology of NAFLD.[13] In addition, decreased testosterone is associated with elevated E2 levels in men, which may be the result of an increased conversion of testosterone to E2. E2 has been discovered to inhibit lipogenesis in male rats by lowering fatty acid synthase and the phosphorylation of acetyl coenzyme A.As a result, E2 may influence the relationship between testosterone and NAFLD.[14]

It has been proven that the severity of liver damage is correlated with a decrease in plasma testosterone levels and a rise in plasma estrogen levels in patients who have liver cirrhosis. In addition to this, it was shown that the levels of prolactin and SHBG, in the blood of patients who had cirrhosis, were significantly raised. The presence of portosystemic shunts in patients with liver cirrhosis is one factor that contributes to the development of hypogonadism.[15] In the current study, low serum Testosterone levels had no effect on SHBG in patients diagnosed with liver cirrhosis owing to substance misuse (alcohol). At least two plasma proteins, SHBG and albumin, bind to testosterone in circulation. The component that has access to the cell and produces androgenic effects is commonly regarded to be the unbound free testosterone. Our study's shortcoming is that we dealt directly with patients, which necessitated a time-consuming and intricate approach for regular assay. On the other hand, it must be considered that the total testosterone level in liver cirrhosis does not accurately reflect testosterone activity due to normal serum SHBG levels.[16] Cross-sectional research of senior men revealed that a rise in total testosterone level was associated with a fifty seven percent reduced probability of the metabolic syndrome diagnosis. In a population of middle- aged Finnish males, low total testosterone and SHBG were found to be predictive with metabolic syndrome. Despite this substantial relationship, causality has not been demonstrated between testosterone and metabolic syndrome.[17,18] In men with chronic liver disease, hypogonadism and overt feminization are frequent clinical manifestations. Associated with these characteristics, it has been discovered that cirrhotic males have a decreased synthesis of testosterone and low plasma concentrations, although only a minority of cirrhotic men appear to have a marginal rise in circulating physiologically active estrogens.[19]

Several earlier studies reported an increase in testosterone concentration with age, while other studies found no change with age. Testosterone in males is primarily derived from peripheral aromatization of circulating androgens, and obesity is known to be a factor in aromatization rate. As our subjects were nonobese and older subjects had significantly lower BMI this may be one reason for the lower serum testosterone levels in our subjects.[20]

CONCLUSION

There are significant age-related changes on the basis of two types of liver cirrhosis in total serum testosterone, their pituitary regulation, or their serum binding by SHBG in men overthe age of forty. However, in this study no effect of sex hormone binding globulin was found. In male patients with liver cirrhosis, low testosterone levels are related with hypogonadism. Male cirrhotic patients may benefit from testosterone replacement therapy to increase muscle mass, but its effect in enhancing muscle activity has to be determined. The treatment's safety and efficacy require additional prospective study.

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