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Commentary

Testosterone rescue for failing livers? Target-trial signals survival gains in hypogonadic men with cirrhosis

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Definitions, rationale, and aims

The testicular hormone testosterone regulates the development and maintenance of male sexual characteristics, including the growth of skeletal muscles and bone tissue, the preservation of a healthy balance of lean-to-fat mass, the improvement of insulin sensitivity and the stimulation of bone marrow to produce red blood cells [1,2]. In males, hypogonadism is defined as testicular failure to produce enough testosterone, sperm or both, resulting in a combination of hypotestosteronaemia and associated clinical manifestations [3]. Approximately 40% of men over the age of 45 and one in two of those in their 80s are hypogonadal, as testosterone levels decrease by 100 ng/dL every 10 years [4,5].

Liver cirrhosis is a condition with a variable etiology that results in a distorted and highly fibrotic architecture of liver tissue, leading to portal hypertension, organ failure and an increased risk of hepatocellular carcinoma (HCC) in some cases [6]. This condition is associated with male hypogonadism (MH). Risk factors for MH in cirrhosis include age, alcohol consumption, duration and severity of liver disease [7]. MH in cirrhosis is multifactorial and includes decreased testosterone synthesis, elevated levels of sex-hormone-binding globulin (SHBG) levels, and hypothalamic-pituitary dysfunction [8]. Low testosterone levels, which indicate MH, may be present in up to 90% of cases of cirrhosis [9]. MH in liver cirrhosis, which falls under the field of "hepatocrinology" [10], is not only a laboratory finding but is also associated with sarcopenia, osteoporosis and anemia [8,11]. However, the effects of testosterone supplementation on clinical outcomes in cirrhosis are not well understood. Men with hypogonadism are more likely to have Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic disorders than healthy individuals [12,13]. MASLD-cirrhosis can develop after neurosurgery or because of diseases affecting the hypothalamic-pituitary tract [14]. Testosterone deficiency may contribute to increased hepatic de novo lipogenesis, decreased lipid secretion from hepatocytes and increased endoplasmic reticulum stress. These effects can be reversed with testosterone replacement therapy (TRT) [12]. Nevertheless, the specific ways in which these molecular mechanisms contribute to adverse liver-related outcomes in cirrhosis remain unclear. Moreover, the published studies on testosterone supplementation in cirrhosis are outdated, underpowered, and primarily focus on measuring biochemical or physiologic markers rather than robust clinical endpoints, such as death, ascites,

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variceal bleeding, or bone fractures. In this commentary, we discuss on a recent study that helps clarifying this topic [15].

Testosterone supplementation in cirrhosis

Given the logistical challenges and ethical concerns of conducting a randomized trial, Tapper, Chen, and Parikh from the University of Michigan, USA, attempted to simulate such a trial using the framework of target-trial emulation with large-scale administrative data [15]. The authors conducted an emulated clinical trial using Medicare claims from the US from 2008 to 2020, which included nearly every outpatient visit, hospital stay, diagnosis code and prescription fill for older Americans or those on federal disability. In their study, they initially identified men who had been newly diagnosed with cirrhosis and who received a new diagnosis of testicular hypofunction within the same 180-day period. This specific time frame established a clear 'time zero', like the randomization point in a traditional trial. To ensure that this was a true 'new user' cohort, any man who had previously filled a testosterone prescription was excluded. Patients who filled in at least one prescription for either transdermal or injectable testosterone within 180 days after the index diagnosis were included in the treatment group, while those who did not were assigned to receive usual care.

Because treatment is never randomly assigned in an observational dataset, the authors used inverse treatment probability weighting with overlap weights to balance more than thirty baseline characteristics, including age, race, a comprehensive list of comorbidities, cirrhosis etiology, prior evidence of hepatic decompensation and concomitant medications such as beta-blockers or insulin. After weighting, the two groups looked remarkably similar: the median age was just under 70 years, roughly half of the men lived in urban zip codes, about one quarter carried an alcohol use disorder code and the prevalence of baseline ascites or hepatic encephalopathy hovered around 12%.

A total of 282 men (7.4% of the analyzed sample, a lower proportion than expected, suggesting a potential selection bias) had MH and initiated TRT. Over the ensuing years, they spent 28.6% of their time actively on therapy compared to only 0.5% in the control arm, confirming a large difference in exposure. The primary composite outcome, which included death from any cause or liver transplantation, occurred less frequently in the testosterone users. After accounting for the competing risk of liver transplantation, the hazard ratio was sub-distributed at 0.92 (95% confidence interval 0.85-0.99). When the components were analyzed separately, the reduction in mortality was decisive for the result, while the transplantation rates were identical at 0.8% in both groups.

Secondary analyses revealed a uniform picture. Individuals receiving testosterone had experienced fewer initial episodes of hepatic decompensation, with a sub-hazard ratio (sHR) of 0.92. This effect was most pronounced for ascites requiring large-volume paracentesis (sHR 0.82) and variceal hemorrhage (sHR 0.67). The number of hospitalizations for overt hepatic encephalopathy was slightly lower, but the difference was not statistically significant. Treatment had no impact on the overall occurrence of osteoporotic or traumatic fractures, nor did it increase the risk of intracranial bleeding. Importantly, concerns that androgen stimulation could promote hepatocellular carcinoma (HCC) were unfounded. The sHR for HCC was 1.09, and the confidence interval comfortably crossed unity. To further verify the findings, the authors analyzed gastrointestinal infections, an outcome less likely to be influenced by sex hormones, and found no correlation, arguing against a significant residual 'healthy user' bias.

Treatment effects varied among different patient subsets. Stratified analyses indicated that men aged 65 years or older, diabetics and patients with ascites at baseline experienced the greatest survival advantage. In diabetics, the mortality sHR decreased to 0.33. However, men with cirrhosis, categorized as alcohol-related, did not seem to benefit from the treatment. In this subgroup, the point estimate for death favored the control arm with an sHR of 1.49. One plausible explanation is that ongoing alcohol consumption, which was not measured in the eligibility data, may accelerate liver injury and diminish the anabolic effects of testosterone, thus abrogating any potential benefit.

The authors acknowledge several limitations associated with claims-based research. The database does not contain any laboratory values, so it is impossible to adjust for Model for End-stage Liver Disease scores or for the actual testosterone concentrations achieved during treatment. Medication adherence is inferred from pharmacy fills, rather than being directly observed. Furthermore, as most of the participants were elderly, it is unclear to what extent the findings are transferable to younger men with liver cirrhosis. Despite these limitations, many of the biases that typically affect observational pharmaco-epidemiology studies were reduced by careful cohort construction, a new-user design and advanced weighting techniques. Taken together, these strategies tend to provide more meaningful information than standard observational studies, even if they are not equivalent to a true randomized clinical trial. Therefore, the findings from this study should be viewed with caution and interest. On the one hand, intramuscular administration of the old nandrolone decanoate to patients with liver cirrhosis - which was mostly of viral origin in the geographical area where one of the authors practiced as a fellow in gastroenterology - was common practice in the early 1980s. On the other hand, most patients at that time died from the supposed complications of cirrhosis per se. However, we lacked either technology or, sometimes, clinical awareness of the notion that HCC may underlie

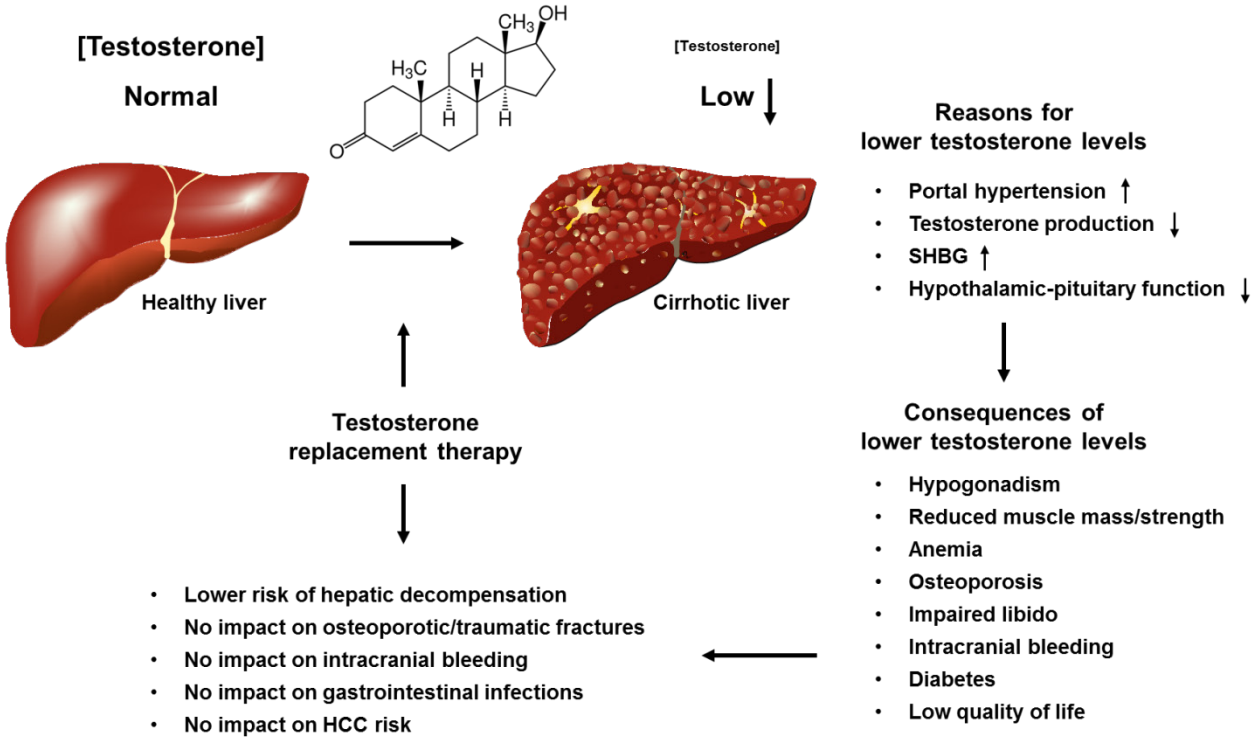

Figure 1. Testosterone replacement in men with cirrhosis

such complications of cirrhosis in many cases. Neither did we measure testosterone values pre- and post-treatment with nandrolone decanoate in our patients with cirrhosis. However, in this regard, the paper by Tapper, et al. provides reassurance that treatment of hypogonadism did not result in any significantly increased HCC risk.

Collectively, the findings published by Tapper and colleagues provide the strongest evidence to date that testosterone replacement can lead to clinically meaningful improvements for a proportion of individuals with cirrhosis and MH (Figure 1).

The consequences of cirrhosis include portal hypertension, increased expression of sex-hormone binding globulin (SHBG), hypothalamic-pituitary dysfunction, and reduced testosterone production, leading to a decrease in testosterone levels. These consequences lead to hypogonadism, reduced muscle mass/strength, anemia, osteoporosis, impaired libido, erectile dysfunction, intracranial bleeding, diabetes and ultimately a poor quality of life. Tapper and colleagues suggest that TRT in cirrhotic men may reduce the overall risk of hepatic decompensation without affecting the frequency of osteoporotic or traumatic fractures, intracranial bleeding, gastrointestinal infections, or the risk of developing hepatocellular carcinoma (HCC) [15].

Implications and research agenda

In conclusion, the study by Tapper et al [15] recommends incorporating regular endocrine screening into standard hepatology evaluations. It also endorses discussing TRT with eligible patients, particularly older individuals without alcohol consumption and with metabolic comorbidities or early ascites [15]. Importantly, a recent study has demonstrated that TRT administered intramuscularly for 12 months can improve the surrogate biomarker of liver fibrosis FIB-4 index in individuals with MH and a higher baseline FIB-4 index [16].

However, only a prospective, adequately powered randomized trial with clear evidence on the etiology of cirrhosis and mechanistic explanations of the action of TRT can dispel the remaining doubts. This trial can also provide guidance on the optimal dosage and route of administration of testosterone, as well as determine whether the lack of apparent benefit in alcohol-related disease is due to disease pathobiology or other factors. Until such a trial is conducted, these results provide a strong argument for clinicians to consider screening all cirrhotic patients for MH and, whenever indicated, consider TRT as part of comprehensive cirrhosis treatment in accordance with good hepatocrinology practices.

Abbreviations

FIB-4: fibrosis-4 index
HCC: hepatocellular carcinoma
MASLD: metabolic dysfunction-associated steatotic liver

disease
MH: male hypogonadism
SHBG: sex-hormone-binding globulin
sHR - sub-hazard ratio
TRT: testosterone replacement therapy

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Conflict of interests

None to declare.

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