Title

Low Testosterone Is Associated With Nonalcoholic Steatohepatitis and Fibrosis Severity in Men

Journal

Clinical Gastroenterology and Hepatology, 19(2)

ISSN

1542-3565

Authors

Sarkar, Monika
Yates, Katherine
Suzuki, Ayako
et al.

Publication Date

2021-02-01

DOI

10.1016/j.cgh.2019.11.053

Peer reviewed

HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2022 February 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2021 February ; 19(2): 400–402.e2. doi:10.1016/j.cgh.2019.11.053.

Low Testosterone Is Associated With Nonalcoholic Steatohepatitis (NASH) and Severity of NASH Fibrosis in Men With NAFLD

Monika Sarkar, MD, MAS[1], **Katherine Yates, ScM**[2], **Ayako Suzuki, MD, Ph.D**[3], **Joel Lavine, MD, Ph.D**[4], **Ryan Gill, MD, Ph.D**[5], **Toni Ziegler, Ph.D**[6], **Norah Terrault, MD, MPH**[1,7], **Sandeep Dhindsa, MD, FACE**[8]

[1]Division of Gastroenterology and Hepatology, University of California, San Francisco, California

[2]Department of Biostats and Epidemiology, Johns Hopkins University,

[3]Division of Gastroenterology and Hepatology, Duke University, Durham, North Carolina

[4]Division of Pediatric Gastroenterology and Hepatology, Columbia University, New York, New York

[5]University of California, San Francisco, Department of Pathology

[6]National Primate Research Center, University of Wisconsin, Madison, Wisconsin

[7]Division of Gastroenterology and Hepatology, University of Southern California, Los Angeles, CA

[8]Division of Endocrinology and Metabolism, Saint Louis University, Saint Louis, Missouri

Keywords

Testosterone; NAFLD; NASH; obese

Correspondence: Monika Sarkar, MD, MAS 400 Parnassus Ave, San Francisco, CA 94143 (415) 353-1888, monika.sarkar@ucsf.edu.
Author contributions: M.S. put forth the hypothesis, planned and analyzed the study, and performed initial manuscript draft. K.Y. and S.D. analyzed data and edited manuscript. T.Z. performed the measurements of testosterone in the samples. N.T. helped to plan the study provided content review and manuscript edits. J.L., A.S. and R.G. provided content review and manuscript edits.

Conflict of Interest:
MS: Site PI for an industry sponsored NAFLD clinical trial (Zydus Pharmaceuticals).
KY: nothing to disclose
AS: nothing to disclose
JL: Consultant for Merck, Novo Nordisk, and Pfizer, grant support from Genfit.
RG: nothing to disclose
TZ: nothing to disclose
NT: Advisory board Intercept; institutionalization grant support Gilead.
SD: Bayer (consultant), site PI for a pharmaceutical multicenter trial (TRAVERSE) to evaluate cardiovascular events after testosterone therapy, sponsored by Abbvie.
No authors have any personal conflicts of interest to disclose.

INTRODUCTION:

With rising prevalence of obesity and diabetes, non-alcoholic fatty liver disease (NAFLD) is now a leading cause of chronic liver disease. One-third of obese or diabetic men have subnormal free and bioavailable testosterone concentrations(1). Several studies have further shown low testosterone to be associated with imaging-confirmed NAFLD in men(2), although it is unknown whether low testosterone confers increased risk of more clinically relevant manifestations of NAFLD, including non-alcoholic steatohepatitis (NASH) and NASH fibrosis. We therefore aimed to evaluate the association of testosterone with histologic features of NAFLD among a representative cohort of men from the multicenter NASH Clinical Research Network (NASH CRN).

METHODS:

NASH CRN participants were selected at random to include the full spectrum of NAFLD, from simple steatosis to NASH with varying severity of fibrosis. The NAFLD Activity Score (NAS) was also calculated (composite score from 0–8 composed of steatosis (0–3), hepatocyte ballooning (0–2) and lobular inflammation scores (0–3)). Fibrosis ranged from stages 0–4. NASH diagnosis included possible or definite NASH. Biopsies were centrally evaluated by NASH CRN pathologists. Testosterone and SHBG were measured from fasting blood samples within 6 months of biopsy. Free and bioavailable (free + albumin bound) testosterone were calculated(3). Covariates included demographics, anthropomorphic and fasting serum lipid and insulin resistance measures. The association of low free testosterone with NAFLD histology was determined by logistic and ordinal logistic regression as appropriate. Additional methodology provided in Supplementary materials.

RESULTS:

Biopsy-confirmed NASH was present in 72% of men, and 18% (n=28) had advanced fibrosis (Table 1). Low free testosterone was present in 26% of men with NAFLD, including 24% of men less than 40 years old. Men with low free testosterone were more likely to have NASH versus simple steatosis (88% vs 67%, p=0.01), as well as advanced fibrosis (27% vs 14%, p=0.07). NASH prevalence increased with lower quartiles of free testosterone (in 88% of men in lowest quartile versus 68% in highest quartile (p=0.03)) (Supplemental Figure 1). Low free testosterone was associated with NASH, independent of age, waist circumference, insulin resistance, and triglycerides (Adjusted OR 3.5; 95% CI 1.01–11.3, p=0.03) and with higher stage of fibrosis (Adjusted OR 2.1, 95% CI 1.0–4.1, p=0.04) (Supplementary Table 1). Free testosterone concentrations in men with and without NASH were 5.3 (3.7–8.9) and 7.2 (5.3–9.8) ng/dl, respectively (p=0.03). Free and bioavailable testosterone concentrations were highly correlated (r=0.98, p<0.001). Low bioavailable testosterone also remained associated with presence of NASH (Adjusted OR 3.7, 95%CI 1.2–12.0, p=0.03) and fibrosis severity (Adjusted OR 2.0, 95%CI 1.0–3.8, p=0.05).

DISCUSSION:

Leveraging data from the NASH CRN Study Cohort we identified low free testosterone levels in a quarter of men with NAFLD, and a third of those with NASH, including nearly a quarter of men under age 40 years. Moreover, low testosterone remained independently associated with presence of NASH (versus simple steatosis), as well as more severe NASH fibrosis. We also selected a conservative cut-off to define “low testosterone” that is below the threshold where hypogonadal symptoms typically develop(4). This is of clinical relevance as NASH is not an entity known to be associated with hypogonadism in men.

Several studies have demonstrated lower testosterone levels in men with NAFLD, and/or an independent association low testosterone with imaging-confirmed NAFLD in men (2, 5). Testosterone replacement in men also improves insulin resistance, lipids, and visceral adiposity, supporting a more direct role of testosterone on metabolic risk factors for NAFLD/NASH (1, 6, 7). Low free testosterone has also been associated with noninvasive markers of fibrosis(8), although the current study is the first to evaluate this association with histologically-confirmed NAFLD. Using “gold standard” LC/MS-MS methodology, we further demonstrated progressively lower testosterone concentrations by NAFLD severity.

The current study has some limitations, including lack of control group without NAFLD, as well as high proportion of men with NASH, likely due to higher suspicion for disease prompting biopsy. As a cross sectional study, causality of low testosterone and NASH could not be evaluated. While testosterone might be protective against NASH, lower testosterone may also reflect worse metabolic health in men. Due to the relatively small number with advanced fibrosis, we lacked power to analyze advanced fibrosis as a dichotomized outcome, although were able to perform a robust analysis of fibrosis severity, including adjustment for comprehensive metabolic parameters.

In conclusion, low free testosterone in men was independently associated with presence and severity of NASH. Testosterone measurements should be considered in future prospective studies of the natural history of NAFLD in men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Grant Support:

The NASH CRN is supported by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK). MS is supported by a K23 from the NIDDK (DK111944). We also acknowledge the UCSF Liver Center (P30 DK026743) for content support.

Abbreviations:

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NASH CRN	NIH/NIDDK NASH Clinical Research Network

NAS	NAFLD Activity Score
SHBG	sex hormone binding globulin
HOMA-IR	homeostasis model assessment of insulin resistance
TG	triglycerides
HDL	high-density lipoprotein cholesterol
LDL	low-density lipoprotein cholesterol

REFERENCES:

1. Dhindsa S, Ghanim H, Batra M, and Dandona P. Hypogonadotropic Hypogonadism in Men With Diabesity. Diabetes Care. 2018;41(7):1516–25. [PubMed: 29934480]
2. Jaruvongvanich V, Sanguankeo A, Riangwiwat T, and Upala S. Testosterone, Sex Hormone-Binding Globulin and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Ann Hepatol. 2017;16(3):382–94. [PubMed: 28425408]
3. Vermeulen A, Verdonck L, and Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84(10):3666–72. [PubMed: 10523012]
4. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–35. [PubMed: 20554979]
5. Sarkar M, VanWagner LB, Terry JG, Carr JJ, Rinella M, Schreiner PJ, et al. Sex Hormone-Binding Globulin Levels in Young Men Are Associated With Nonalcoholic Fatty Liver Disease in Midlife. The American journal of gastroenterology. 2019;114(5):758–63. [PubMed: 30730350]
6. Dhindsa S, Ghanim H, Batra M, Kuhadiya ND, Abuaysheh S, Sandhu S, et al. Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men With Type 2 Diabetes. Diabetes care. 2016;39(1):82–91. [PubMed: 26622051]
7. Kapoor D, Goodwin E, Channer KS, and Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. European journal of endocrinology/European Federation of Endocrine Societies. 2006;154(6):899–906.
8. Fujihara Y, Hamanoue N, Yano H, Tanabe M, Akehi Y, Nomiyama T, et al. High sex hormone-binding globulin concentration is a risk factor for high fibrosis-4 index in middle-aged Japanese men. Endocr J. 2019.

Table 1.

Cohort Characteristics Among Men with Biopsy-Confirmed NAFLD by Free Testosterone (Free T) Level.

	All men (n=159)	Low Free T (n=41)	Normal Free T (n=118)	p value
Age (years)	47 (37–55)	48 (38–59)	47 (37–54)	0.21
Race, n (%)				
White	131 (82)	33 (80)	98 (83)	
Asian	14 (9)	4 (10)	10 (8)	
Black	3 (3)	2 (5)	1 (1)	0.30
Other	11 (6)	2 (5)	9 (8)	
Hispanic, n (%)	24 (15)	5 (12)	19 (16)	0.55
Body mass index (kg/cm^2)	33 (30–35)	34 (32–37)	32 (30–35)	0.14
Obesity, n (%)	113 (71)	33 (81)	80 (68)	0.12
Waist circumference (cm)	108 (100–118]	114 (101–121)	107 (100–115)	0.07
Waist-to-hip ratio	0.98 (0.94–1.02)	0.99 (0.94–1.02)	0.98 (0.95–1.02)	0.46
Total cholesterol (mg/dL)	184 (162–221)	183 [156–219]	187 (162–222)	0.60
HDL (mg/dL)	38 (33–43)	38 (34–42)	38 (33–44)	0.93
LDL (mg/dL)	115 (90–140)	119 (89–138)	114 (91–143)	0.68
Triglycerides (mg/dL)	166 (106–238)	143 (97–239)	170 (107–235)	0.20
Dyslipidemia, n (%)	134 (84)	35 (85)	99 (84)	0.93
Type 2 Diabetes, n (%)	41 (26)	18 (44)	23 (19)	0.002
HOMA-IR	4.4 [2.9–6.5]	4.7 (3.2–7.6)	3.8 (2.7–5.3)	0.45
Total testosterone (ng/dL)	285 [195–391]	149 (117–212)	321 (253–422)	<0.001
Free testosterone (ng/dL)	5.7 [4.0–9.1]	3.1 (2.5–3.7)	7.7 (5.4–9.9)	<0.001
Bioavailable testosterone (ng/dL)	139 [96–216]	77 (57–89)	183 (132–241)	<0.001
Sex hormone binding globulin (nmol/L)	25 [16–38]	29 (16–46)	24 (16–36)	0.28
NASH, n (%)	115 (72)	36 (88)	79 (67)	0.01
NAFLD Activity Score (NAS)	4 [3–6]	5 (4–6)	4 (3–5)	0.001
Advanced fibrosis (stages 3–4), n (%)	28 (18)	11 (27)	17 (14)	0.07

Height, weight, waist and hip measurements were taken in duplicate while standing and wearing light clothing and averaged for analyses. Waist circumference was measured midway between the iliac crest and bottom of the rib cage. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (meters) squared. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: (fasting glucose [mg/dL] fasting insulin [mU/L])/405. Dyslipidemia was defined as triglycerides > 150ng/dL, high-density lipoprotein (HDL) < 40ng/dL, low-density lipoprotein (LDL) > 130ng/dL, or total cholesterol > 200ng/dL. Obesity was defined as BMI ≥ 30 kg/m2. Low free testosterone defined as <4ng/dl.