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Original Article

Metabolic Dysfunction-Associated Steatotic Liver Disease and Vascular Complications: Associations with Serum Testosterone Levels in a Korean Multicenter Male Cohort

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Background/Aims: We investigated the associations of testosterone levels with metabolic dysfunction-associated steatotic liver disease (MASLD) and vascular complications in a large Korean male cohort. Despite the high global prevalence of MASLD and significant morbidity from cardiovascular disease, the interplay among testosterone levels, MASLD, and vascular outcomes remains unclear, particularly in Asian populations.

Methods: This cross-sectional study analyzed 1,167 men from the Korean Health Screening-Based MASLD Registry. MASLD was defined as imaging-confirmed steatosis with metabolic dysfunction. Log2-transformed testosterone levels were analyzed using logistic regression adjusted for metabolic risk factors to evaluate associations with MASLD, advanced fibrosis (Fibrosis-4 index [FIB-4] ≥1.3), carotid plaques, and cerebrovascular accidents (CVAs).

Results: Among the 1,167 men (mean age 57.0 years), 730 (62.6%) had MASLD. These patients had lower testosterone levels than non-MASLD men did (223.5 ng/dL vs 347.5 ng/dL; p<0.001) and showed adverse metabolic features. Higher testosterone levels were independently associated with reduced risk of MASLD (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.85 to 0.94; p<0.001). Among the MASLD patients, higher testosterone levels were linked to a significantly lower prevalence of carotid plaques (OR, 0.77; 95% CI, 0.73 to 0.81) and CVAs (OR, 0.75; 95% CI, 0.67 to 0.82). The associations remained robust across sensitivity analyses with adjustments for obesity, diabetes, and dyslipidemia. No significant association was observed with advanced fibrosis (FIB-4 ≥1.3).

Conclusions: Low testosterone levels are independently associated with MASLD and its vascular complications but not with advanced fibrosis. Serum testosterone levels may serve as a practical biomarker for metabolic and vascular risk stratification in MASLD patients, warranting validation in prospective and interventional studies. (ClinicalTrials.gov identifier NCT06843421)
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Key Words: Metabolic dysfunction-associated steatotic liver disease; Testosterone; Carotid artery diseases; Cerebrovascular accident; Biomarkers

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most prevalent chronic liver disease worldwide, affecting roughly one-quarter of the global population.[1,2] Its clinical significance lies not only in its potential to progress to advanced liver fibrosis and cirrhosis but also in its strong association with systemic metabolic comorbidities, including obesity, type 2 diabetes, and cardiovascular disease (CVD).[3] Indeed, the burden of MASLD-related morbidity and mortality is largely driven by extrahepatic complications, with CVD representing the leading cause of death among affected patients.[4]

Testosterone, a key sex hormone in men, plays a crucial role in regulating metabolic function, body composition, and vascular health.[5] Low serum testosterone, or hypogonadism, has been linked to components of metabolic syndrome, such as insulin resistance, central obesity, and dyslipidemia.[6,7] A growing body of evidence suggests an inverse relationship between testosterone levels and the risk of MASLD, although the precise mechanisms are still being elucidated.[8,9] Furthermore, testosterone has direct effects on the cardiovascular system, influencing endothelial function, blood pressure, and inflammatory markers, which are all implicated in the development of atherosclerosis and cerebrovascular events.[10]

While the individual associations between low testosterone and MASLD, and between MASLD and CVD, are well-documented, the synergistic interplay between these three conditions is not fully understood, especially in Asian populations. The metabolic and genetic profiles of Asian individuals may differ from those of Western populations, potentially influencing the clinical presentation and progression of these diseases.

In this context, we conducted a large-scale, multicenter, cross-sectional study within a Korean male health-screening cohort to investigate the independent associations of serum testosterone levels with the presence of MASLD and its vascular complications. We hypothesized that low testosterone would be a significant risk factor for MASLD and that this association would extend to a higher prevalence of carotid plaque and cerebrovascular accidents (CVAs) among men with MASLD, even after accounting for conventional metabolic risk factors. This study aimed to provide novel insights into the systemic role of testosterone in metabolic and vascular health, highlighting its potential utility as a biomarker for risk stratification in male MASLD patients.

MATERIALS AND METHODS

1. Study population

This study was conducted using data from the Korean Health Screening-Based Metabolic Dysfunction-Associated Steatotic Liver Disease Registry (K-MASLD Registry; ClinicalTrials.gov identifier NCT06843421). The registry was designed as a multicenter retrospective cohort to evaluate the association of hepatic steatosis with CVD incidence and other chronic metabolic diseases. Study participants were recruited from university-affiliated health screening centers. Although data collection was initially planned across six hospitals, complete data were ultimately obtained from four centers, yielding a total of 3,466 participants between January 2020 and December 2023.

Recruitment was based on abdominal ultrasonography: (1) individuals with imaging-confirmed hepatic steatosis who met the criteria for metabolic dysfunction were classified as the MASLD group, whereas (2) participants without ultrasonographic evidence of hepatic steatosis were classified as the non-MASLD control group, irrespective of the presence of metabolic risk factors.

To enhance statistical power for group comparisons, MASLD and non-MASLD participants were enrolled in approximately a 1:1 ratio; therefore, the prevalence of MASLD in this registry does not reflect its true prevalence in the general population. For the present analysis, we excluded women (n=1,401), individuals with excessive alcohol consumption (n=70), and those without available serum testosterone data (n=828). The final study population consisted of 1,167 men, of whom 730 had MASLD and 437 did not (Fig. 1).

The study protocol was approved by the Institutional Review Board of Ajou University Hospital (AJOUIRB-DB-2024-310) and by the respective IRBs of the participating institutions. Owing to the retrospective nature of the study and the use of de-identified health screening data, the requirement for informed consent was waived.

2. Data collection and definitions

Baseline demographic and clinical variables, including age, body mass index (BMI), hypertension, diabetes mellitus, hyperlipidemia, liver function tests, lipid profile, platelet count, hemoglobin A1c, thyroid function, and sex hormones, were obtained from the health screening database. MASLD was defined according to current international consensus criteria, based on evidence of hepatic steatosis on ultrasonography in the presence of metabolic dysfunction, and after exclusion of other chronic liver diseases and excessive alcohol intake.[11] Fibrosis-4 index (FIB-4) was calculated as an estimate of advanced fibrosis, with

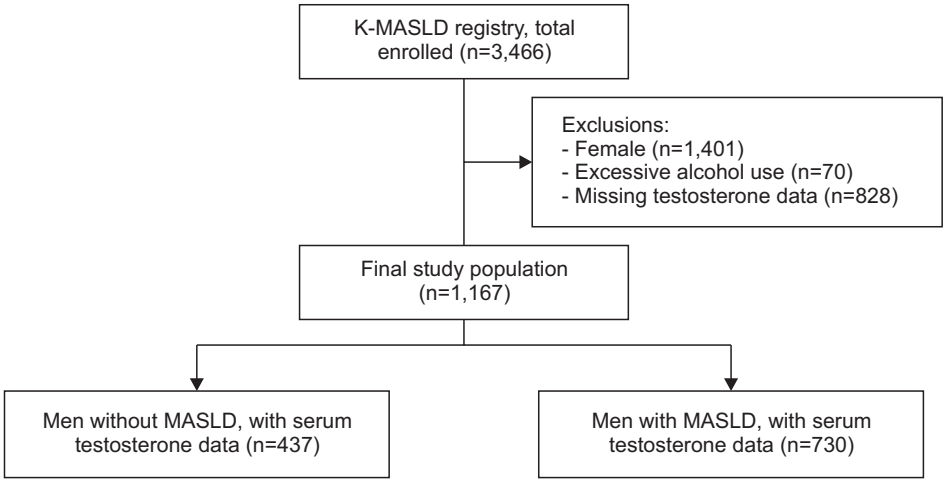


Fig. 1. Flowchart of study population selection. From the K-MASLD Registry (n=3,466), women (n=1,401), individuals with excessive alcohol use (n=70), and those without available serum testosterone data (n=828) were excluded. The final study population consisted of 1,167 men, including 437 without MASLD and 730 with MASLD. K-MASLD, Korean Health Screening-Based Metabolic Dysfunction-Associated Steatotic Liver Disease Registry; MASLD, metabolic dysfunction-associated steatotic liver disease.

a cutoff of 1.3 used to stratify risk groups.[12] Carotid plaque was assessed by carotid ultrasonography performed as part of the screening program. CVA events were defined as the presence of relevant ICD-10 codes recorded in clinical encounters up to January 2025. Testosterone was analyzed as a continuous variable after log2 transformation. In addition to analyses using log2-transformed testosterone as a continuous variable, we performed supplementary categorical analyses using a clinically established cutoff for low testosterone (<300 ng/dL), commonly used to define biochemical hypogonadism.[13]

3. Statistical analysis

Continuous variables are presented as mean±standard deviation and categorical variables as numbers and percentages. Differences between groups were compared using the Student t-test or chi-square test, as appropriate. Univariable logistic regression analyses were performed to evaluate associations between clinical variables and outcomes (MASLD, FIB-4 ≥1.3, carotid plaque, and CVAs). To reduce multicollinearity, variables representing overlapping clinical domains were screened, and only the most representative or statistically significant variable was included in the multivariable logistic regression models. For instance, alanine aminotransferase (ALT) was selected as the representative marker among liver enzymes (aspartate aminotransferase [AST], ALT, γ-glutamyltransferase [GGT], and alkaline phosphatase), and glycated hemoglobin (HbA1c) was included instead of diabetes status to represent glycemic control. All analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and a two-tailed p-value <0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics

A total of 1,167 male participants with available testosterone measurements were included in the analysis, comprising 730 patients with MASLD (62.6%) and 437 without MASLD (37.4%). The overall mean age was 56.97±9.71 years, and there was no significant difference between groups (56.6 years vs 57.6 years; p=0.083). Patients with MASLD showed significantly higher BMI compared to those without MASLD (26.61±3.20 kg/m^2 vs 23.81±2.59 kg/m^2; p<0.001). The prevalence of hypertension (43.1% vs 29.1%; p<0.001), diabetes mellitus (20.4% vs 14.7%; p=0.017), and hyperlipidemia (41.4% vs 28.9%; p<0.001) was also higher in the MASLD group. Alcohol consumption also differed significantly between groups (p=0.015); the MASLD group had a higher proportion of mild drinkers (58.6% vs 56.5%), whereas moderate-to-severe drinking was more prevalent in the non-MASLD group (19.0% vs 12.9%). Regarding liver-related parameters, MASLD patients had higher AST (34.28±16.45 U/L vs 31.07±15.60 U/L; p=0.001), ALT (39.37±23.68 U/L vs 27.57±14.45 U/L; p<0.001), and GGT levels (52.58±46.82 U/L vs 39.35±46.14 U/L; p<0.001). Alkaline phosphatase was also slightly higher in the MASLD group (71.15±18.26 U/L vs 68.78±18.54 U/L; p=0.034). No differences were observed in total bilirubin levels between groups. Albumin was marginally higher in MASLD patients (4.82±0.29 g/dL vs 4.74±0.28 g/dL; p<0.001), while platelet counts were also significantly higher (248.14±54.18×10^9/L vs 238.83±57.09×10^9/L; p=0.005) (Table 1).

Metabolic parameters demonstrated adverse profiles in MASLD patients, including higher HbA1c (5.99%±0.86% vs 5.73%±0.77%; p<0.001), triglycerides (156.52±91.52 mg/dL vs 104.08±67.11 mg/dL; p<0.001), and low-density lipoprotein (LDL) cholesterol (123.56±42.35 mg/

Table 1. Baseline Characteristics

Variable	Overall (n=1,167)	No MASLD (n=437)	MASLD (n=730)	p-value
Age, yr	56.97±9.71	57.60±10.71	56.59±9.05	0.083
BMI, kg/m^2	25.56±3.27	23.81±2.59	26.61±3.20	<0.001
Hypertension	441 (37.9)	127 (29.1)	314 (43.1)	<0.001
Diabetes mellitus	213 (18.3)	64 (14.7)	149 (20.4)	0.017
Dyslipidemia	428 (36.7)	126 (28.9)	302 (41.4)	<0.001
Alcohol consumption				0.015
No	315 (27.0)	107 (24.5)	208 (28.5)	
Mild	675 (57.8)	247 (56.5)	428 (58.6)	
Moderate	177 (15.2)	83 (19.0)	94 (12.9)	
AST, U/L	33.08±16.20	31.07±15.60	34.28±16.45	0.001
ALT, U/L	34.95±21.48	27.57±14.45	39.37±23.68	<0.001
GGT, U/L	47.62±46.98	39.35±46.14	52.58±46.82	<0.001
ALP, U/L	70.26±18.40	68.78±18.54	71.15±18.26	0.034
Total bilirubin, mg/dL	0.92±0.41	0.93±0.43	0.92±0.40	0.799
Albumin, g/dL	4.79±0.29	4.74±0.28	4.82±0.29	<0.001
Platelet count, ×10^9/L	244.65±55.45	238.83±57.09	248.14±54.18	0.005
HbA1c, %	5.89±0.84	5.73±0.77	5.99±0.86	<0.001
Triglyceride, mg/dL	136.88±86.98	104.08±67.11	156.52±91.52	<0.001
HDL cholesterol, mg/dL	51.73±13.72	57.27±15.65	48.41±11.19	<0.001
LDL cholesterol, mg/dL	121.08±41.99	116.94±41.09	123.56±42.35	0.009
Total cholesterol, mg/dL	187.02±45.58	183.72±45.10	188.84±45.79	0.106
Testosterone, ng/dL	269.93±263.68	347.46±284.43	223.52±238.87	<0.001
TSH, μIU/mL	2.47±3.28	2.44±2.38	2.48±3.71	0.819
Free T4, ng/dL	1.31±0.22	1.33±0.26	1.30±0.19	0.015

Data are presented as the mean±SD or number (%).
MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone; Free T4, free thyroxine.
p-values were obtained by using Student t-test for continuous variables and the chi-square test for categorical variables.

Table 2. Univariable and Multivariable Logistic Regression Analyses of Factors Associated with MASLD (n=1,167)

Variable	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.99 (0.98–1.00)	0.083	1.02 (1.00–1.04)	0.027
BMI	1.45 (1.37–1.54)	<0.001	1.37 (1.29–1.47)	<0.001
Hypertension, yes	1.84 (1.43–2.38)	<0.001	1.31 (0.93–1.83)	0.118
Diabetes mellitus, yes	1.49 (1.09–2.07)	0.014		
Dyslipidemia, yes	1.74 (1.35–2.25)	<0.001	1.17 (0.83–1.66)	0.400
AST	1.01 (1.01–1.02)	0.001		
ALT	1.04 (1.03–1.05)	<0.001	1.03 (1.02–1.04)	<0.001
GGT	1.01 (1.00–1.01)	<0.001		
ALP	1.01 (1.00–1.01)	0.034		
Total bilirubin	0.96 (0.72–1.29)	0.799		
Albumin	2.87 (1.88–4.41)	<0.001	2.79 (1.57–5.00)	<0.001
Platelet	1.00 (1.00–1.01)	0.006	1.00 (1.00–1.00)	0.400
HbA1c	1.58 (1.33–1.92)	<0.001	1.38 (1.12–1.71)	0.003
Triglyceride	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
HDL cholesterol	0.95 (0.94–0.96)	<0.001	0.97 (0.96–0.99)	<0.001
LDL cholesterol	1.00 (1.00–1.01)	0.009	1.01 (1.00–1.01)	0.001
Log2 testosterone	0.89 (0.85–0.92)	<0.001	0.89 (0.85–0.94)	<0.001
Free T4	0.50 (0.28–0.88)	0.018	0.74 (0.35–1.48)	0.413

MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Free T4, free thyroxine.

dL vs 116.94±41.09 mg/dL; p=0.009). Conversely, high-density lipoprotein (HDL) cholesterol levels were significantly lower in the MASLD group (48.41±11.19 mg/dL vs 57.27±15.65 mg/dL; p<0.001). Total cholesterol levels did not differ significantly between groups. Endocrine parameters revealed that serum testosterone levels were significantly lower in patients with MASLD (223.52±238.87 ng/dL vs 347.46±284.43 ng/dL; p<0.001). Thyroid function parameters showed no differences in thyroid-stimulating hormone between groups, while Free T4 was slightly lower in MASLD patients (1.30±0.19 ng/dL vs 1.33±0.26 ng/dL; p=0.015) (Table 1).

2. Association between testosterone and MASLD

Univariable logistic regression analysis (Table 2) showed that an increase in BMI (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.37 to 1.54; p<0.001), hypertension (OR, 1.84; 95% CI, 1.43 to 2.38; p<0.001), diabetes (OR, 1.49; 95% CI, 1.09 to 2.07; p=0.014), and hyperlipidemia (OR, 1.74; 95% CI, 1.35 to 2.25; p<0.001) were associated with higher risk of MASLD. In addition, increases in AST, ALT, GGT, HbA1c, triglycerides, and LDL-cholesterol were

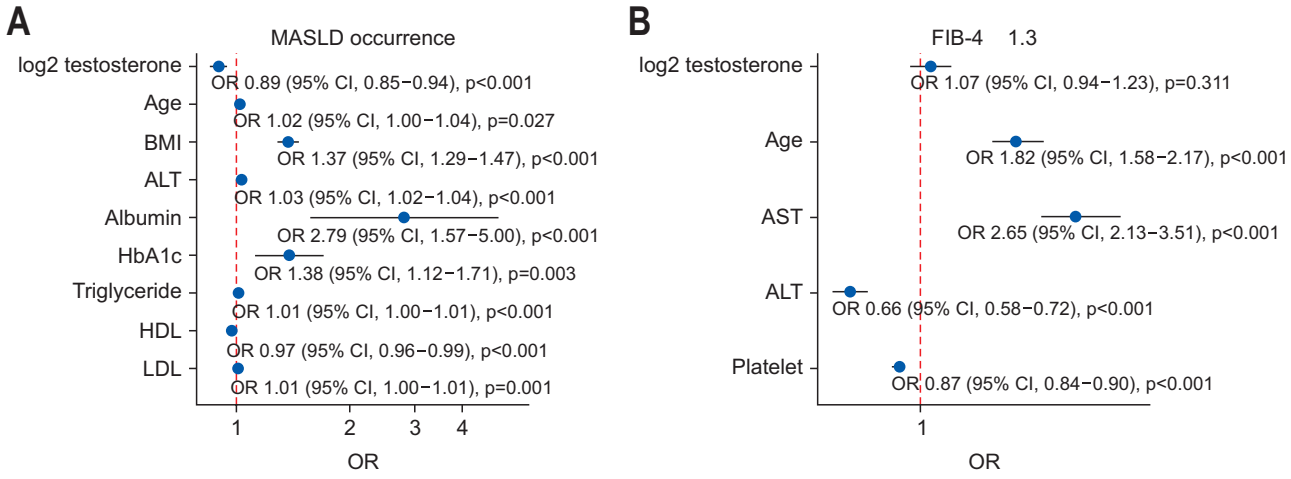


Fig. 2. Forest plots of independent risk factors for presence of MASLD (A) and FIB-4 ≥1.3 (B). MASLD, metabolic dysfunction-associated steatotic liver disease; FIB-4, Fibrosis-4 index; BMI, body mass index; ALT, alanine aminotransferase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; CI, confidence interval; AST, aspartate aminotransferase.

Table 3. Univariable and Multivariable Logistic Regression Analyses of Factors Associated with FIB-4 ≥1.3 in Patients with MASLD (n=730)

Variable	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.16 (1.13–1.19)	<0.001	1.82 (1.58–2.17)	<0.001
BMI	0.98 (0.81–1.20)	0.865		
Hypertension, yes	0.76 (0.21–2.64)	0.662		
Diabetes mellitus, yes	0.47 (0.07–2.90)	0.422		
Dyslipidemia, yes	1.59 (0.44–5.94)	0.480		
AST	2.63 (2.10–3.53)	<0.001	2.65 (2.13–3.51)	<0.001
ALT	0.66 (0.58–0.73)	<0.001	0.66 (0.58–0.72)	<0.001
GGT	1.00 (0.99–1.02)	0.801		
ALP	0.98 (0.95–1.02)	0.321		
Total bilirubin	1.13 (0.34–3.78)	0.846		
Albumin	1.28 (0.22–7.46)	0.780		
Platelet	0.87 (0.84–0.90)	<0.001	0.87 (0.84–0.90)	<0.001
HbA1c	1.10 (0.45–2.70)	0.836		
Triglyceride	1.00 (0.99–1.01)	0.702		
HDL cholesterol	1.01 (0.96–1.06)	0.794		
LDL cholesterol	1.00 (0.99–1.02)	0.873		
Log2 testosterone	1.11 (0.95–1.30)	0.192	1.07 (0.94–1.23)	0.311
Free T4	1.00 (0.09–13.12)	1.000		

FIB-4, Fibrosis-4 index; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Free T4, free thyroxine.

associated with higher risk, whereas an increase in HDL-cholesterol was associated with lower risk (OR, 0.95; 95% CI, 0.94 to 0.96; p<0.001). Notably, an increase in log2-transformed testosterone was associated with lower risk of MASLD (OR, 0.89; 95% CI, 0.85 to 0.92; p<0.001).

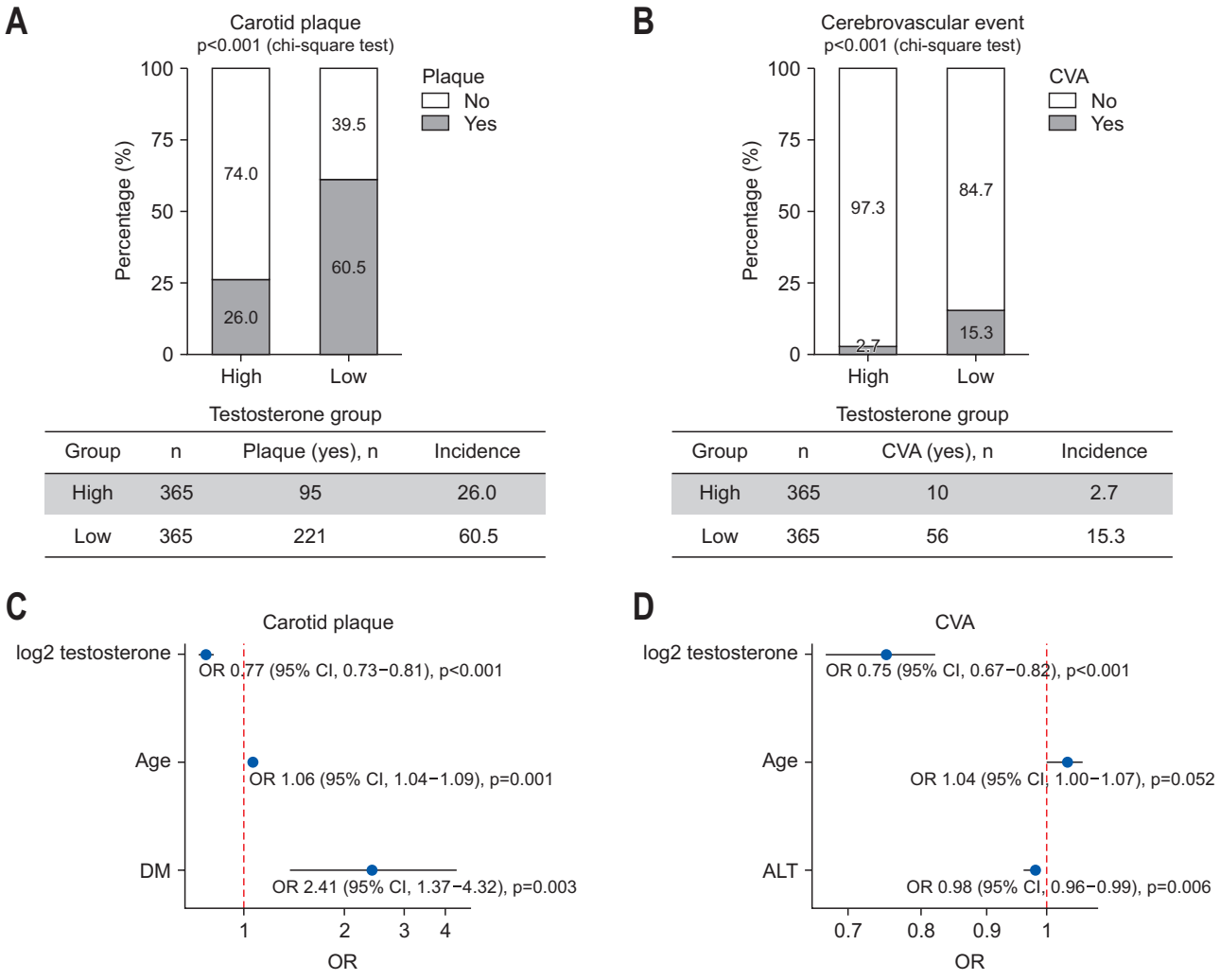
In the multivariable model, independent predictors of MASLD included older age, higher BMI, ALT, albumin, HbA1c, and triglycerides, whereas HDL-cholesterol remained protective. Importantly, log2-transformed testosterone remained independently associated with lower risk of MASLD (OR, 0.89; 95% CI, 0.85 to 0.94; p<0.001). These findings are illustrated in Fig. 2A. In categorical analyses, low testosterone level in the hypogonadal range was independently associated with a higher risk of MASLD (adjusted OR, 1.98; 95% CI, 1.47 to 2.68; p<0.001), consistent with the primary continuous analyses (Supplementary Table 1).

Consistent associations were observed in age-stratified analyses (<60 years vs ≥60 years), in which lower testosterone levels were associated with higher odds of MASLD in both age groups (Supplementary Table 2).

3. Factors associated with FIB-4 in MASLD patients

In MASLD patients, factors associated with FIB-4 were assessed (Table 3). Univariable analysis showed that older age and higher AST were associated with higher risk of FIB-4 ≥1.3, while higher ALT and platelet counts were associated with lower risk. Other metabolic parameters were not significantly associated.

In the multivariable model, older age (OR, 1.82; 95% CI, 1.58 to 2.17; p<0.001) and higher AST (OR, 2.65; 95% CI, 2.13 to 3.51; p<0.001) remained independent predictors of FIB-4 ≥1.3. Conversely, higher ALT (OR, 0.66; 95% CI, 0.58 to 0.72; p<0.001) and higher platelet counts (OR, 0.87; 95%



Group	n	Plaque (yes), n	Incidence
High	365	95	26.0
Low	365	221	60.5

Group	n	CVA (yes), n	Incidence
High	365	10	2.7
Low	365	56	15.3

Fig. 3. Comparison of carotid plaque and cerebrovascular event incidences, and forest plots of independent risk factors between the high- and low-testosterone groups of the MASLD patients. (A) Incidence of carotid plaques according to the testosterone groups. (B) Incidence of cerebrovascular events according to the testosterone groups. (C) Forest plot of independent risk factors for carotid plaques. (D) Forest plot of independent risk factors for CVAs. CVA, cerebrovascular accident; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; ALT, alanine aminotransferase.

CI, 0.84 to 0.90; p<0.001) were associated with lower risk. By contrast, log2-transformed testosterone was not significantly associated with FIB-4 in either model. These results are summarized in Fig. 2B. Similarly, in categorical analyses, testosterone level (<300 ng/dL) was not independently associated with FIB-4 ≥1.3, consistent with the findings of the continuous analyses (Supplementary Table 3).

In age-stratified analyses (<60 years vs ≥60 years), log2-transformed testosterone was not significantly associated with FIB-4 ≥1.3 in multivariable models in either age group, indicating no consistent age-dependent association between testosterone levels and fibrosis risk (Supplementary Table 4).

4. Association between testosterone and carotid plaque in MASLD patients

In MASLD patients, the prevalence of carotid plaque differed significantly by testosterone status (Fig. 3A). Carotid plaque was observed in 26.0% of the high testosterone group compared with 60.5% of the low testosterone group (p<0.001). Univariable regression (Table 4) showed that older age, hypertension, diabetes, hyperlipidemia, higher HbA1c, and LDL-cholesterol were associated with carotid plaque. Importantly, log2-transformed testosterone was strongly associated with a lower risk (OR, 0.79; 95% CI, 0.75 to 0.83; p<0.001). In the multivariable model, older age (OR, 1.06; 95% CI, 1.04 to 1.09; p<0.001) and diabetes (OR, 2.41; 95% CI, 1.37 to 4.32; p=0.003) remained independent risk factors, while log2-transformed testosterone remained an independent protective factor (OR, 0.77; 95% CI, 0.73 to 0.81; p<0.001). These associations are depicted in Fig. 3C. In categorical analyses, low testosterone level (<300 ng/dL) was independently associated with a higher risk of carotid plaque (adjusted OR, 3.70; 95% CI, 2.62 to 5.26; p<0.001), consistent with the primary continuous analyses (Supplementary Table 5).

5. Association between testosterone and CVA in MASLD patients

The incidence of CVA also differed according to testosterone level (Fig. 3B). CVA occurred in 2.7% of the high testosterone group and in 15.3% of the low testosterone group (p<0.001). Univariable analysis (Table 5) showed that older age and some liver enzyme levels were associated with CVA. However, these associations did not remain significant after adjustment. By contrast, log2-transformed testosterone consistently showed an independent inverse association with CVA (OR, 0.75; 95% CI, 0.67 to 0.82; p<0.001). These findings are summarized in Fig. 3D. In categorical analyses, low testosterone level (<300 ng/dL) was independently associated with a higher risk of CVA (adjusted OR, 7.53; 95% CI, 3.55 to 18.60; p<0.001), consistent with the primary continuous analyses (Supplementary Table 6).

Table 4. Logistic Regression Analyses of Factors Associated with Carotid Plaque Formation in Patients with MASLD (n=730)

Variable	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.06 (1.04–1.08)	<0.001	1.06 (1.04–1.09)	<0.001
BMI	0.94 (0.90–0.99)	0.014	0.96 (0.91–1.02)	0.200
Hypertension, yes	1.54 (1.14–2.07)	0.004	1.40 (0.96–2.05)	0.084
Diabetes mellitus, yes	2.39 (1.66–3.47)	<0.001	2.41 (1.37–4.32)	0.003
Dyslipidemia, yes	1.45 (1.08–1.95)	0.015	0.98 (0.68–1.41)	0.905
AST	1.00 (0.99–1.01)	0.394		
ALT	0.99 (0.99–1.00)	0.076		
GGT	1.00 (1.00–1.00)	0.484		
ALP	1.00 (0.99–1.01)	0.523		
Total bilirubin	0.77 (0.53–1.12)	0.179		
Albumin	1.24 (0.75–2.08)	0.400		
Platelet	1.00 (1.00–1.00)	0.855		
HbA1c	1.33 (1.11–1.59)	0.002	0.95 (0.73–1.22)	0.682
Triglyceride	1.00 (1.00–1.00)	0.999		
HDL cholesterol	1.01 (1.00–1.03)	0.068		
LDL cholesterol	1.00 (0.99–1.00)	0.024	1.00 (1.00–1.01)	0.446
Log2 testosterone	0.79 (0.75–0.83)	<0.001	0.77 (0.73–0.81)	<0.001
Free T4	0.28 (0.12–0.64)	0.003	0.61 (0.25–1.51)	0.287

MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Free T4, free thyroxine.

Table 5. Logistic Regression Analyses of Clinical and Biochemical Factors Associated with Cerebrovascular Accidents in MASLD Patients (n=730)

Variable	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.05 (1.02–1.08)	0.003	1.04 (1.00–1.07)	0.052
BMI	0.98 (0.90–1.06)	0.583	1.03 (0.93–1.14)	0.552
Hypertension, yes	1.36 (0.82–2.26)	0.235	1.24 (0.70–2.20)	0.458
Diabetes mellitus, yes	1.40 (0.76–2.46)	0.263	1.07 (0.55–1.99)	0.841
Dyslipidemia, yes	0.91 (0.54–1.52)	0.725		
AST	0.97 (0.95–0.99)	0.021		
ALT	0.97 (0.95–0.99)	0.001	0.98 (0.96–0.99)	0.006
GGT	1.00 (0.99–1.00)	0.888		
ALP	1.00 (0.99–1.02)	0.674		
Total bilirubin	0.68 (0.33–1.31)	0.270		
Albumin	0.60 (0.24–1.45)	0.262		
Platelet	1.00 (1.00–1.00)	0.959		
HbA1c	1.10 (0.82–1.42)	0.515		
Triglyceride	1.00 (0.99–1.00)	0.056	1.00 (0.99–1.00)	0.150
HDL cholesterol	1.02 (1.00–1.04)	0.095	1.00 (0.97–1.02)	0.960
LDL cholesterol	1.00 (0.99–1.00)	0.575		
Log2 testosterone	0.75 (0.68–0.83)	<0.001	0.75 (0.67–0.82)	<0.001
Free T4	1.04 (0.27–4.01)	0.950		

MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Free T4, free thyroxine.

DISCUSSION

In this large multicenter study of Asian men, we demonstrated that lower serum testosterone levels were independently associated with an increased risk of MASLD, as well as a higher prevalence of carotid plaque and CVA. By contrast, testosterone levels were not significantly associated with FIB-4, a surrogate marker of liver fibrosis. These findings suggest that lower serum testosterone levels are associated with MASLD and vascular complications, while being less clearly associated with fibrosis progression. To our knowledge, this is among the first studies to evaluate these associations simultaneously in a well-characterized Asian cohort.

Our results extend prior evidence linking testosterone deficiency to metabolic dysfunction and fatty liver disease. Several population-based studies, including analyses from the National Health and Nutrition Examination Survey cohort, have shown that low testosterone is associated with a higher prevalence of nonalcoholic fatty liver disease independent of obesity and insulin resistance.[14-16] Our findings are consistent with these observations and confirm that lower testosterone is inversely associated with MASLD in Asian populations, supporting the notion that lower testosterone levels are linked to hepatic steatosis through shared metabolic pathways involving visceral adiposity, insulin resistance, and dyslipidemia.

In contrast, the relationship between testosterone and liver fibrosis has remained controversial. Experimental studies in animal models have indicated that androgen deprivation can exacerbate hepatic stellate cell activation and fibrogenesis.[17] However, clinical studies have been inconsistent, with some reporting inverse associations between testosterone and fibrosis[18] and others showing null results.[15] In our study, testosterone was not significantly associated with FIB-4 in either univariable or multivariable models, suggesting that testosterone may have a more prominent effect on metabolic drivers of MASLD rather than fibrosis progression itself. These discrepancies may also reflect differences in study design, fibrosis assessment methods, and underlying population characteristics.

Perhaps the most notable finding of our analysis is the strong and independent inverse association between testosterone levels and vascular complications, including carotid plaque and CVA, in men with MASLD. This aligns with prior epidemiologic studies and meta-analyses showing that low testosterone has been consistently associated with atherosclerosis, stroke, and CVD.[10,19,20] Several mechanisms may underlie these associations. Testosterone has been shown to improve insulin sensitivity, increase muscle mass, reduce visceral fat deposition, and exert anti-inflammatory effects.[21-23] Moreover, experimental data indicate that testosterone enhances endothelial function and reduces arterial stiffness.[24,25] These mechanisms may partly account for the observed associations between testosterone levels and vascular outcomes.

From a clinical perspective, our findings highlight the potential role of testosterone as a biomarker for identifying MASLD patients at higher risk of vascular complications, in addition to established metabolic risk factors. However, whether correction of testosterone deficiency has a causal impact on these outcomes remains uncertain. Large-scale longitudinal studies and randomized controlled trials are needed to clarify the temporal relationship and to assess whether interventions addressing testosterone deficiency could improve metabolic or vascular outcomes in MASLD populations.

This study has important strengths, including its large sample size, multicenter design, and the use of log-transformed testosterone to evaluate quantitative and linear associations. Furthermore, we simultaneously examined hepatic and vascular outcomes, providing a comprehensive assessment of testosterone-related risks in MASLD. However, several limitations should be noted. First, the cross-sectional design precludes causal inference. Second, testosterone was measured at a single time point. Although this approach is commonly used in large-scale epidemiologic studies, it does not account for diurnal variation or within-individual variability over time, which may limit clinical interpretability and lead to measurement error. Consequently, the observed associations should be interpreted with caution, and future studies incorporating repeated morning measurements are warranted. In addition, information on specific endocrine disorders or testosterone-related therapies was not systematically available, and residual confounding by unmeasured endocrine factors cannot be excluded. Finally, fibrosis was assessed using FIB-4 rather than histology or elastography, which may have limited sensitivity for detecting early-stage fibrosis.

In conclusion, our findings demonstrate that low testosterone is independently associated with increased risk of MASLD, carotid plaque, and CVA, but not with liver fibrosis as assessed by FIB-4, in a large cohort of Asian men. These results suggest that testosterone may serve as a useful biomarker of metabolic and vascular risk in MASLD populations. Future prospective and interventional studies are warranted to validate these associations and to explore whether therapeutic strategies targeting testosterone deficiency could improve long-term outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: H.J.C. Data acquisition: S.H.K., H.Y.C., S.A.B., E.K., S.K.N., S.J.K., D.K., H.R.A., H.K., S.S.K. Data analysis and interpretation: H.J.C., S.H.K., H.Y.C., S.J.K., D.K. Drafting of the manuscript: H.J.C. Critical revision of the manuscript for important intellectual content: S.H.K., H.Y.C., S.A.B., E.K., S.K.N., S.J.K., D.K., H.R.A., H.K., S.S.K., J.Y.C., S.K.B., Y.K.J., H.J.Y. Methodology: H.J.C., S.H.K., H.Y.C. Statistical analysis: H.J.C. Obtained funding: H.J.C., H.J.Y. Administrative, technical, or material support: J.Y.C., S.K.B., Y.K.J., H.J.Y. Study supervision: H.J.C., H.J.Y., Y.K.J., S.K.B. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.

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DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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