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Original Article

Sarcopenia in Indian Males Having Clinically Significant Liver Fibrosis in Type 2 Diabetes: A Tertiary-Centre Cross-Sectional Study to Estimate the Prevalence and Associated Factors

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Abstract

Objectives: The study aimed to measure the prevalence of sarcopenia in male individuals with type 2 diabetes having clinically significant liver fibrosis and to identify the determinants of sarcopenia. **Methods**: A cross-sectional study was conducted among male individuals aged 18–65 years with type 2 diabetes and liver stiffness measurement (LSM) ≥8 kPa, as measured by transient elastography (FibroScan®). Individuals were divided into sarcopenic and nonsarcopenic groups using the 2019 Asian Working Group for Sarcopenia criteria. **Results**: Among 131 males with significant liver fibrosis in type 2 diabetes, 43 (32.8%) had sarcopenia. Between the sarcopenic and non-sarcopenic groups, significant differences were observed in body weight (Kg) (62.6 vs 69.7, $p < 0.001$) the median duration of diabetes (months) (96 vs. 60, $p = 0.008$), glycated hemoglobin (HbA1c, 8.8% vs. 7.9%, $p = 0.007$), and liver fibrosis (LSM score, 10.3 kPa vs. 9.8 kPa, $p = 0.028$). The adjusted odds ratios (ORs) for liver fibrosis and body weight in the development of sarcopenia were 1.165 (95% CI, 1.051–1.292) and 0.933 (95% CI, 0.894–0.974), respectively. **Conclusion**: Individuals with sarcopenia had a longer duration of diabetes and poorer glycemic control; lower body weight and higher grades of liver fibrosis were independent factors contributing to the same.

Keywords: Type 2 Diabetes, Males, Clinically Significant Liver Fibrosis, Sarcopenia, Testosterone

Introduction

A common, albeit potentially fatal medical illness, diabetes mellitus, has become more prevalent in recent decades, making it a significant public health concern worldwide[1]. We have moved from a digit-specific management focused solely on controlling plasma glucose to a more disease-specific approach that addresses the complications of diabetes. Apart from the well-known common micro- and macrovascular complications, entities like liver disease are often overlooked[2]. Liver fibrosis is a progressive and often asymptomatic complication in individuals with type 2 diabetes, primarily driven by metabolic dysfunction-associated steatotic liver disease (MASLD)[3]. Type 2 diabetes not only predisposes individuals to MASLD but also significantly increases the risk of progression to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). A recent individual participant-level meta-analysis demonstrated that type 2 diabetes is an independent risk factor for hepatic decompensation and HCC in patients with MASLD, regardless of other traditional risk factors[4]. Additionally,

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transient elastography data from the Indian population reveal that a substantial proportion of adults with type 2 diabetes—nearly 23%—may have undiagnosed advanced liver fibrosis[5].

Sarcopenia, the progressive decline in skeletal muscle mass and strength, is increasingly recognized as a complication in individuals with type 2 diabetes[6]. Insulin resistance impairs the PI3K/Akt/mTOR anabolic pathway, reducing muscle protein synthesis and promoting degradation[6]. Hormonal alterations, including reduced testosterone, growth hormone, and insulin-like growth factor 1 (IGF-1) levels, are also observed in patients with diabetes and negatively affect muscle maintenance[7]. A growing body of evidence suggests a bidirectional relationship between sarcopenia and liver fibrosis. Chronic liver inflammation, insulin resistance, and metabolic dysregulation contribute to muscle degradation, while reduced muscle mass exacerbates hepatic insulin resistance and systemic inflammation, thereby accelerating liver damage[8,9]. In addition to these shared mechanisms, mitochondrial dysfunction and altered myokine signaling, including decreased irisin and IGF-1, play pivotal roles in impairing hepatic and muscular homeostasis.

Although the intertwined pathophysiology of sarcopenia and liver fibrosis is known, there is a paucity of data from India in this area. Hence, we decided to measure the prevalence of sarcopenia in male individuals with type 2 diabetes having liver fibrosis, and to find out the predictors of the same, including serum total testosterone level.

Methods

Study Design and Patients

A cross-sectional study design was performed, including 131 male individuals with type 2 diabetes (defined as per the criteria proposed by the American Diabetes Association 2023 and classified according to the World Health Organization 2019 statement) aged 18 to 65 years attending the Diabetes Clinic of Nil Ratan Sircar Medical College and Hospital, Kolkata, India (under the Department of Endocrinology). All the participants had liver fibrosis of ≥8 kPa (kilopascal). All the patients were from lower-middle and upper lower socioeconomic classes, as classified by the Revised Kuppuswamy Socioeconomic Status Scale[10]. Clinical and anthropometric measurements, assessment of sarcopenia using handgrip strength, appendicular skeletal mass, and gait speed, and biochemical workups were performed in all patients.

Persons who suffered acute metabolic complications (diabetic ketoacidosis, hyperglycemic hyperosmolar state, lactic acidosis, etc.) in the last 3 months or had severe chronic illness; who were taking any drugs that could affect muscular function or have hepatotoxic potential or have therapeutic use for MASLD; person who had neuropathy (either diabetes-related or for other reasons) or neuromuscular disorders, abnormal liver functions

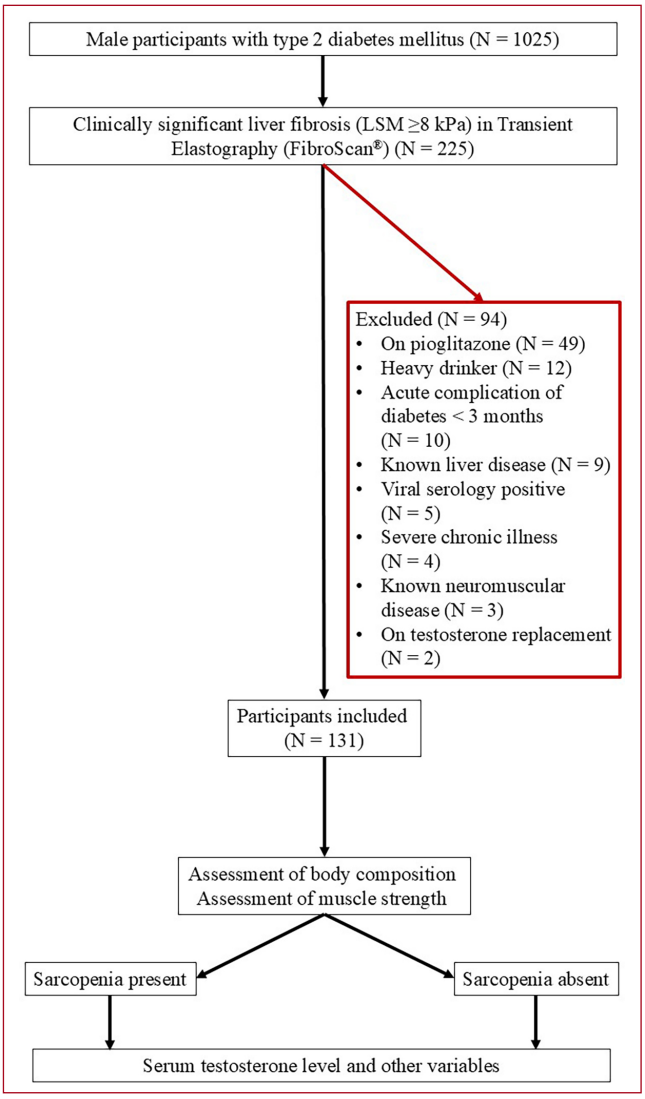

Figure 1. The flow of the current study, LSM – Liver Stiffness Measurement.

(aspartate aminotransferase, alanine aminotransferase >5 times of upper normal limit) or liver diseases caused by conditions other than MASLD including alcohol intake (>210 grams per week) were excluded from the study. Also, the persons who were known to have hypogonadism with or without hormone replacement therapy had been screened out before the assessment of muscular mass and function. The study flow has been depicted in Figure 1.

Assessment of physical activity

The International Physical Activity Questionnaire Short Form was used to assess individuals' physical activity levels. Participants provided one week of activity data via interview before being included in the study. Walking,

moderate-intensity activities, and vigorous-intensity activities were the three types of activity assessed; frequency (days per week) and duration (minutes per day) were collected separately for each type. Data were presented as continuous variables after being converted into Metabolic Equivalent (MET) minutes per day for each level of activity (3.3 METs for walking, 4.0 METs for moderate-intensity, and 8.0 METs for vigorous-intensity), and the final data were generated by summing all activity METs and represented as MET minutes per week[11].

Assessment of protein intake, sleep duration, and smoking

Protein intake was assessed using a dietary recall method based on individuals' usual meal patterns over the last 7 days by an experienced nutritionist before inclusion in the study. We used the variable as weekly protein intake in grams; dividing it into daily intake did not accurately reflect actual intake because some people avoided non-vegetarian meals on certain days of the week due to religious beliefs.

The recall method was used to collect sleep duration data, and the average daily duration was calculated from the weekly data.

The participants were divided into smoker and nonsmoker groups. Nonsmokers were defined as those who had smoked no cigarettes ever or in the last 12 months or less than 1 cigarette per day for the last 12 months before the study.

Liver Stiffness Measurement

Liver Stiffness Measurement (LSM) was performed by a single operator using transient elastography (FibroScan® Mini+ 430 model) on the right lobe of the liver, with the participant lying supine and the right arm in maximal abduction. After 10 successful measurements per patient (with an appropriate probe), an LSM value ≥8.0 kPa was used as the cut-off, indicating clinically significant liver fibrosis (CSLF), given its high positive predictive value. A value of ≥13.0 kPa was taken as a marker of cirrhosis[12].

Measurement of hand grip strength

Individuals were tested for handgrip strength in their dominant hand using the Jamar Plus dynamometer in a seated position with 90° elbow flexion during a maximum-effort isometric contraction. Final grip strength was calculated as the mean of three consecutive measurements taken at 15-minute intervals and expressed in kilograms (Kg)[13].

Measurement of skeletal mass

The Bioelectric Impedance Analyzer (Tanita RD545, TANITA Corporation, Tokyo, Japan) was used to measure body weight, body mass index (BMI), and body composition via multi-frequency bioelectrical impedance analysis (BIA). Prior to the measurement, each participant was instructed to abstain from tea, coffee, and alcohol for 8 hours, fast for 4 hours (no dry fasting for religious reasons or other causes), and avoid exercise for the last 12 hours. Two hours before the test, each participant was instructed to drink 500–1000 ml of water, take off any metal jewellery, wear light clothing to protect their privacy, stand barefoot on the platform without using any lotion or oil on their feet, and hold the hand electrode in their outstretched arms away from their bodies. The Appendicular Skeletal Mass (ASM) was calculated for each patient as the sum of upper- and lower-limb skeletal mass and adjusted by dividing with height squared (ASM/height^2)[13].

Assessment of physical performance

A 6-meter walk test was conducted to assess physical performance. Patients were asked to walk at a normal pace without deceleration, and a timer was set to measure the time to cover a 6-meter distance. The average time was calculated from two consecutive performances, and gait speed was expressed as meters per second (m/s).

Definition of Sarcopenia

Sarcopenia is defined by the Asian Working Group for Sarcopenia (AWGS) 2019 criteria, which involve low grip strength, low height-adjusted Appendicular Skeletal Mass (ASM/height^2), and/or low physical performance. Persons having grip strength <28 Kg and ASM/height^2 <7 Kg/m^2 or 6-meter walk speed < 1 m/s were grouped in sarcopenia, and those who had 6-meter walk speed < 1 m/s along with grip strength <28 Kg and ASM/height^2 <7 Kg/m^2 were classified as severe sarcopenia[13].

Measurement of Total Testosterone and other blood parameters

Serum total testosterone assay was done from the fasting samples drawn in the morning and assessed by Chemiluminescence immunoassay (CLIA) with SIEMENS ADVIA Centaur TSTII kit (Siemens Healthcare Diagnostics Inc.) in ADVIA Centaur® XP Immunoassay System. A second sample was examined after 4 weeks, when testosterone was low (<250 ng/dl) in the first sample. Between the two samples, the lowest value was used in the study. Liver function was assessed by chemiluminescence on the Thermo Fisher Scientific KONELAB PRIME 60. Glycated hemoglobin (HbA1c) was measured using High Performance Liquid Chromatography (HPLC) using the HLC®-723GX Automated Glycohemoglobin Analyzer.

Statistical Analysis

Study participants were divided into sarcopenic and nonsarcopenic groups based on the AWGS 2019 criteria. The normality of the data was tested by the Kolmogorov-Smirnov test. The descriptive statistics for all independent variables were reported as medians with interquartile ranges (IQRs).

Variables	Overall (N = 131)	Sarcopenia present (N = 43, 32.8%)	Sarcopenia absent (N = 88, 67.2%)	*p*-value
Age [years] (Median, IQR)	53 (45 – 60)	57 (49 – 60.5)	51.5 (45 – 60)	0.063§
Body weight [Kg] (Median, IQR)	67.3 (60 – 78)	62.6 (55.2 – 75.3)	69.7 (62.3 – 79.1)	<0.001¥
Duration of diabetes [months] (Median, IQR)	72 (24 – 120)	96 (60 – 144)	60 (24 – 120)	0.008§
Weekly protein intake [gm] (Median, IQR)	170 (135 – 210)	150 (130 – 195)	170 (135 – 211.3)	0.222§
IPAQ [MET-minutes/week] (Median, IQR)	3360 (1426 – 5526)	3146 (1501.5 – 4696.5)	3253 (1486 – 5733)	0.407§
Sleep duration [hours] (Median, IQR)	7 (6 – 8)	7 (6 – 7)	7 (6 – 8)	0.274§
Smoking, N (%)	37 (28.2%)	11 (25.6%)	26 (29.5%)	0.684Ψ
Use of Insulin, N (%)	28 (21.4%)	13 (30.2%)	15 (17%)	0.112Ψ
HbA1c [%] (Median, IQR)	8.2 (7.4 – 9.5)	8.8 (7.9 – 9.8)	7.9 (7.1 – 9)	0.007§
LSM score [kPa] (Median, IQR)	10.1 (9 – 12.6)	10.3 (9.5 – 13.5)	9.8 (8.7 – 11.9)	0.028§
Testosterone [ng/dl] (Median, IQR)	488.2 (368.1 – 608)	504.8 (406.4 – 585.8)	477.2 (343.8 – 623)	0.555¥
Hand grip strength [Kg] (Median, IQR)	26.9 (23.8 – 31.6)			
ASM/height^2 [Kg/m^2] (Median, IQR)	7.3 (6.4 – 8.2)			
6-meter walk speed [m/sec.] (Median, IQR)	1.05 (0.9 – 1.2)			

Table 1. The median and interquartile range (IQR) of independent variables for overall study participants, sarcopenic, and nonsarcopenic groups. *p*-value was calculated from the median differences of the variables between the sarcopenic and nonsarcopenic groups. ASM – Appendicular Skeletal Mass, IPAQ – International Physical Activity Questionnaire, HbA1c – Glycated hemoglobin, kPa – Kilopascal, LSM – Liver Stiffness Measurement, MET – Metabolic Equivalent, N – Number. § Mann-Whitney U test, Ψ Chi-square test, ¥ Independent-samples t-test.

Data was analyzed using the Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for Windows, SPSS, Inc., Chicago, IL, USA. An independent-samples t-test was used to compare the sarcopenic and nonsarcopenic groups for variables that followed a normal distribution (testosterone level), whereas the Mann-Whitney U test was used for nonparametric data. Comparisons of qualitative data, such as insulin use and smoking status, were made using the Chi-square test. A p-value of less than or equal to 0.05 was considered as the indicator of statistical significance.

The univariate model in binary logistic regression with age, body weight, duration of diabetes, weekly protein intake, physical activity, sleep duration, smoking status, use of insulin, HbA1c level, LSM score, and testosterone level was used to estimate the crude Odds ratio (OR) with 95% confidence intervals (CI) for the presence of sarcopenia. The model was further adjusted for variables (age, body weight, duration of diabetes, use of insulin, HbA1c) with p-values < 0.1 in the univariate model. The goodness-of-fit of the model was assessed using Nagelkerke's pseudo R2 (0.302), and the model's accuracy was 73.3%.

Pearson correlation coefficient (**r**) was calculated between independent continuous variables and individual parameters of sarcopenia assessment. A *p*-value of less than or equal to 0.05 was considered as the indicator of statistical significance.

Result

Overall Statistics

As per the selection criteria, all study participants (N = 131) were male. Their median age was 53 years. The median body weight was 67.3 Kg. The participants had a median duration of diabetes of 72 months, a median HbA1c of 8.2%, and a median LSM of 10.1 kPa. The median testosterone level was 488.2 ng/dl (Table 1).

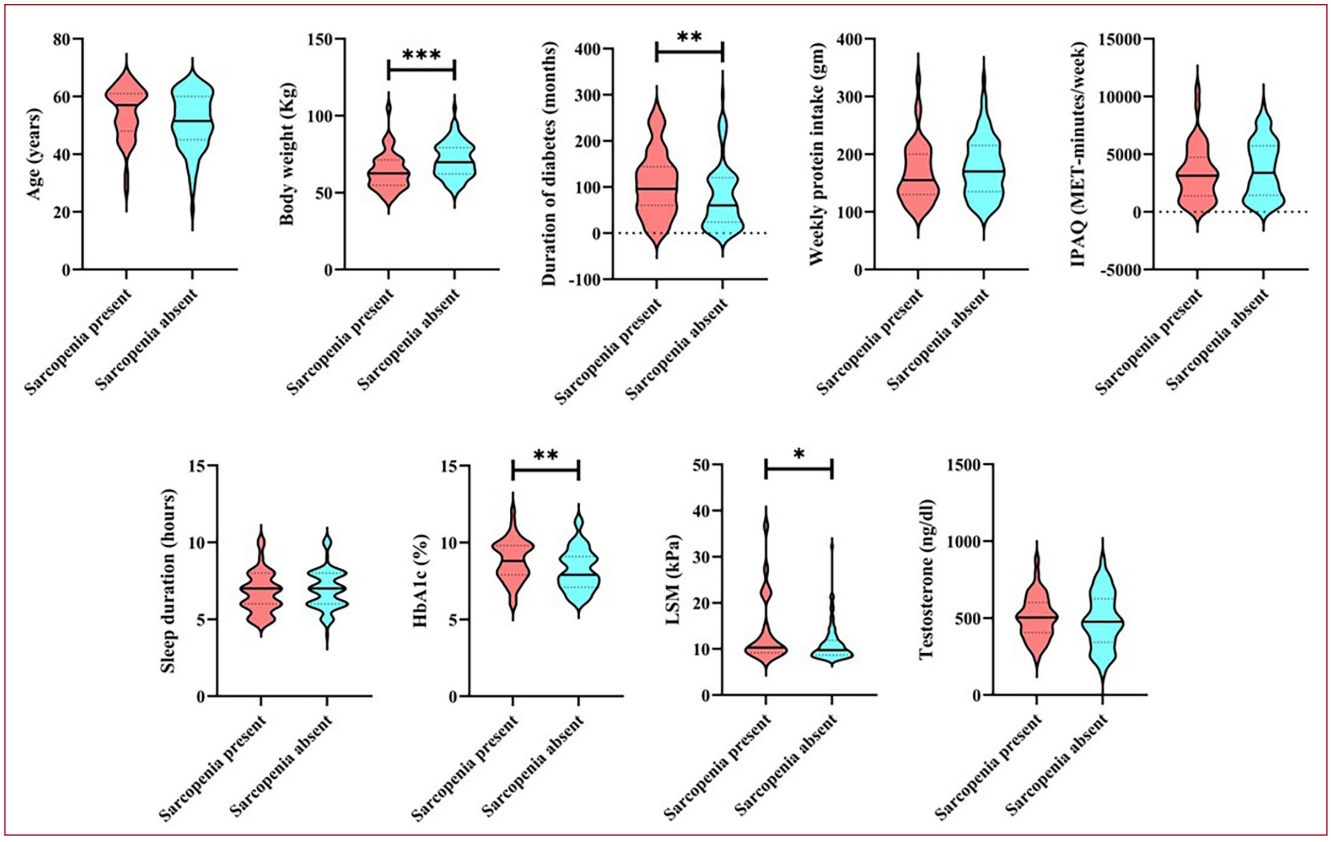

Figure 2. Comparison of the sarcopenic and nonsarcopenic groups in terms of independent variables, *p <0.05, **p < 0.01, ***p <0.001, IPAQ – International Physical Activity Questionnaire, HbA1c – Glycated hemoglobin, kPa – Kilopascal, LSM – Liver Stiffness Measurement, MET – Metabolic Equivalent.

Prevalence of sarcopenia

The median of hand grip strength was 26.9 Kg, ASM/height^2 was 7.3 Kg/m^2, and the median speed of the 6-meter walk test was 1.05 m/sec. 53.4% (70 out of 131) of participants had hand grip strength below 28 Kg, and 35.1% (46 out of 131) had ASM/height^2 below 7 Kg/m^2. Thirty-seven of 131 individuals had a walking speed of less than 1 m/s (28.2%). Forty-three individuals out of 131 (32.8%) met the definition of having sarcopenia according to the 2019 AWGS criteria, and 7% (9 out of 131) were classified as severe sarcopenia (Table 1, Supplementary Figure 1).

Comparison between groups

In the comparison of independent variables between sarcopenic and nonsarcopenic groups, body weight, duration of diabetes, HbA1c level, and LSM score had statistically significant differences (62.6 Kg vs 69.7 Kg, p < 0.001; 96 months vs 60 months, p = 0.008; 8.8% vs 7.9%, p = 0.007; 10.3 kPa vs 9.8 kPa, p = 0.028, respectively) (Table 1, Figure 1) whereas the age of the participants, weekly protein intake, physical activity, sleep duration, smoking status, use of insulin, and testosterone levels did not show any significant difference between the groups. When dividing into CSLF and cirrhosis groups (LSM ≥8 kPa and ≥13 kPa, respectively), 30.1% of individuals had sarcopenia in the CSLF group and 42.9% in the cirrhosis group (Supplementary Figure 2).

Calculating the Odds

In binary logistic regression with univariate analysis, body weight [OR 0.941, 95% CI (0.906 – 0.976)], duration of diabetes [OR 1.006, 95% CI (1.001 – 1.012)], HbA1c [OR 1.435, 95% CI (1.08 – 1.905)], and LSM score [OR 1.1, 95% CI (1.024 – 1.182)] had statistically significant ORs. Age and insulin use had p-values < 0.1 in the univariate model. In multivariate analysis (adjusted for age, body weight, duration of diabetes, use of insulin, HbA1c), the grades of liver fibrosis, as measured by LSM

	Variables	Crude OR (95% CI)	Adjusted OR# (95% CI) pseudo R^2 0.302*
Sarcopenia present	Age (years)	1.04 (0.997 – 1.084) p = 0.068	
	Body weight (Kg)	0.941 (0.906 – 0.976) p = 0.001	0.933 (0.894 – 0.974) p = 0.001
	Duration of diabetes (months)	1.006 (1.001 – 1.012) p = 0.02	
	Weekly protein intake (gm)	0.996 (0.989 – 1.004) p = 0.301	
	IPAQ (MET-minutes/week)	1.0 (1.0 – 1.0) p = 0.422	
	Sleep duration (hours)	0.863 (0.643 – 1.158) p = 0.326	
	Smoking (Yes)	1.22 (0.535 – 2.781) p = 0.636	
	Use of Insulin (Yes)	0.474 (0.202 – 1.116) p = 0.087	
	HbA1c (%)	1.435 (1.08 – 1.905) p = 0.013	
	LSM (kPa)	1.1 (1.024 – 1.182) p = 0.009	1.165 (1.051 – 1.292) p = 0.004
	Serum Testosterone (ng/dl)	1.001 (0.998 – 1.003) p = 0.607	

Table 2. Binary logistic regression analysis for crude and adjusted Odds ratios (OR) with 95% confidence intervals (CI) estimation for sarcopenia (# adjusted for age, body weight, duration of diabetes, use of insulin, HbA1c) (* Nagelkerke's pseudo R^2 for Goodness-of-fit). BMI – Body Mass Index, IPAQ – International Physical Activity Questionnaire, HbA1c – Glycated hemoglobin, kPa – Kilopascal, LSM – Liver Stiffness Measurement, MET – Metabolic Equivalent.

[adjusted OR 1.165, 95% CI (1.051–1.292)], became a strong determinant of sarcopenia. Also, the adjusted OR of body weight was 0.933 [95% CI (0.894 – 0.974)] (Table 2).

Correlation for individual components

While comparing the independent variables with individual components of assessing sarcopenia, a moderate positive correlation was present between body weight and ASM/height^2 (**r** = 0.445, p <0.001), a weak negative correlation was found for HbA1c and hand grip strength (**r** = - 0.3, p <0.001), and a weak negative correlation was found between LSM score and grip strength (**r** = - 0.189, p = 0.03), also with ASM/height^2 (**r** = - 0.199, p = 0.023) (Supplementary Figure 3). Testosterone level had a weak positive correlation with 6-meter walking speed (**r** = 0.217, p = 0.013) (Supplementary Figure 3).

Use of insulin

A total of 28 (21.4%) participants were using insulin when they were included in the study; of them, 46.4% (13 out of 28) had sarcopenia. On the other hand, 29.1% (30 out of 103) had sarcopenia who were not using insulin at the study point (Table 1, Supplementary Figure 4).

Discussion

The prevalence of sarcopenia among the elderly population (≥ 60 years) from India is 39.2%, and among individuals aged 35–70 years is 28%[14,15]. Even though there is greater loss of muscle mass and function in the aged population, sarcopenia is no longer a disease that happens only in the elderly; muscle ages alongside other chronic diseases like diabetes, even before biological aging. Apart from this, the prevalence of sarcopenia varies widely across populations, ethnicities, environments, dietary habits, and activity levels, as well as with the criteria used to define it. We found the prevalence to be 32.8% in type 2 diabetes with CSLF, with 7% classified as severe sarcopenia (Supplementary Figure 1). Although no such Indian research has used a similar study design, previous studies showed that there was a higher prevalence of

sarcopenia (according to AWGS 2019 criteria) even in a relatively younger set of patients suffering from diabetes. One study from New Delhi estimated a prevalence of sarcopenia as 18.8% among patients with type 2 diabetes with a mean age of 46.2 years[16]. Another recent study from the same place showed a prevalence of sarcopenia as 53% among patients with a mean age of 47.8 years[17]. These high prevalences underscore the significance of sarcopenia as a common comorbidity in Indian patients with type 2 diabetes irrespective of biological aging.

A meta-analysis by Ai Y, et al. showed the prevalence of sarcopenia in type 2 diabetes to be 6.3 – 47.1% overall and 16% by the definition proposed by AWGS, but there was very high interstudy heterogenicity depending on the study population and the method of sarcopenia assessment, like, 17% in BIA, 17% in dual-energy X-ray absorptiometry (DXA), and 47% by computed tomography (CT) scan[18]. Though the consensus committee recommendation by Morley JE, et al did not support the use of BIA to define sarcopenia in clinical trials, BIA is still used as it has multiple advantages, e.g. – low cost, no radiation exposure, minimum technical difficulty, and a precision of 2 – 4% compared to DXA (1 – 4%) and CT scan (1 – 3%)[19]. Multifrequency BIA devices can evaluate sarcopenia, as they correlate well with DXA-measured ASM[13,20,21].

In our study, the median age had no statistically significant difference between the sarcopenic and non-sarcopenic groups (Table 1). This aligns with prior research indicating that, while age is a recognized risk factor, it may not always differ significantly across cross-sectional studies after controlling for other variables, such as diabetes duration or comorbidities[22,23]. We included males up to 65 years of age in our study to control for confounders, including age-related sarcopenia[13]. Moreover, previous studies suggested that the age-related decline in testosterone levels is more pronounced after age 60–70 years[24,25].

Individuals with sarcopenia had significant lower mean body weight (62.6 Kg vs 69.7 Kg, p < 0.001), suggesting that higher body weight may have a protective role in maintaining muscle mass[17]. Also, in this study, body weight showed a moderate positive correlation with ASM/height2, with an adjusted OR of 0.933 for the development of sarcopenia (Table 2, Supplementary Figure 3). However, very high body weight reduces muscle mass and function, resulting in sarcopenic obesity.

A significant finding was a longer duration of diabetes among individuals with sarcopenia (96 months vs 60 months; p = 0.008) (Table 1, Figure 2). Participants with sarcopenia also had higher HbA1c levels (8.8% vs 7.9%, p = 0.007), indicating poorer glycemic control (Table 1, Figure 2). This supports existing evidence that prolonged hyperglycemia and diabetes duration are associated with muscle deterioration, possibly due to chronic inflammation, metabolic dysregulation, and muscle catabolism driven by increased oxidative stress[22,26].

Elevated LSM scores in sarcopenic groups (10.3 kPa vs 9.8 kPa, p = 0.028) suggest a link between liver fibrosis and muscle loss, consistent with findings that liver dysfunction may contribute to sarcopenia via metabolic alterations (Table 1, Figure 2). Compared to non-NAFLD, the prevalence of sarcopenia is significantly increased in NAFLD and NASH (8.7% vs 17.9% and 35.0%, respectively)[27,28]. The percentage of individuals experiencing sarcopenia was higher in the cirrhotic group (42.9%) than in the CSLF (30.1%) (Supplementary Figure 2), divided as per LSM values (≥13 kPa and ≥ 8 kPa, respectively)[14,29].

Body weight [OR 0.941, 95% CI (0.906 - 0.976)], diabetes duration [OR 1.006, 95% CI (1.001 - 1.012)], HbA1c [OR 1.435, 95% CI (1.08 - 1.905)], and LSM score [OR 1.1, 95% CI (1.024 - 1.182)] all had statistically significant ORs in univariate analysis (Table 2). This indicates that poor glycemic control substantially increases sarcopenia risk, consistent with prior literature emphasizing the role of hyperglycemia in muscle degradation[26]. Liver fibrosis, as measured by LSM, also showed a significant association [adjusted OR 1.165, 95% CI (1.051–1.292)] (Table 2), corroborating studies that link liver health to muscle mass[27].

In the meta-analysis by Ai Y et al.[18], age, HbA1c, and duration of diabetes were independent predictors of sarcopenia, with Odds ratios of (OR 1.16; 95% CI, 1.06 – 1.27), (1.69; 95% CI, 1.01 – 2.83), (1.31; 95% CI, 0.75 – 2.27), respectively. In their study, Zang F et al. found the prevalence of sarcopenia to be 18.4% in the Chinese population and 16.2% in the US population, with skeletal muscle assessed by DXA and liver stiffness by vibration-controlled transient elastography (VCTE). In the Chinese cohort, 20% had type 2 diabetes, and there was a statistically significant difference in mean LSM score (kPa) between the non-sarcopenic and sarcopenic groups (6.3 vs 6.9, p < 0.001). Liver fibrosis had an OR of 1.27 (95% CI, 1.04 – 1.54). Age and HbA1c did not differ statistically between these groups. On the other hand, the US cohort showed significant differences in mean age (years) and HbA1c (%) (42 vs 48, p = 0.002; 5.6 vs 5.8, p = 0.006, respectively). 20% of this cohort had type 2 diabetes. Liver fibrosis had an OR of 1.79 (95% CI, 1.12 – 2.86)[30]. Sung MJ et al. conducted a cross-sectional study with persons having liver fibrosis measured by FIB4 and NAFLD score in type 2 diabetes and found a 24.3% prevalence of sarcopenia in 309 samples. Age (years) (60.9 vs 68.2, p <0.001) and FIB4 score (1.41 vs 1.63, p = 0.009) were significantly different in non-sarcopenic and sarcopenic groups, respectively. Age, BMI, and FIB4 score (OR 1.817; 95% CI, 1.18–2.797) were independent predictors of sarcopenia in their model. There was no difference in HbA1c level between the two groups[31].

In contrast to evaluation for hypogonadism, we used the lowest serum testosterone value when a second sample

was taken after the first value was <250 ng/dl. Inability to measure sex hormone-binding globulin (SHBG), which may alter the total testosterone level (falsely high), was the primary reason for this deviation from the usual practice. Now, testosterone levels were lower in participants with sarcopenia, but the difference was not significant in the present study. Some prior research indicates that testosterone may not be the sole hormonal factor influencing sarcopenia in populations with diabetes[22]. The role of testosterone in preventing sarcopenia in liver disease is largely debated[32]. A study by Sinclair et al.[33] demonstrated an increase in muscle mass after intramuscular testosterone therapy for 12 months in liver cirrhosis with low baseline testosterone. They concluded that the potential impact of testosterone on muscle health in the background of liver cirrhosis requires large-scale investigative studies. In our study, testosterone had a weak positive correlation with gait speed (**r** 0.217; p = 0.013) (Supplementary Figure 3). It did not correlate with handgrip strength. These findings can be explained by the types of muscle fibers involved in the activities. Walking typically engages slow-twitch muscle fibers (type I); by contrast, handgrip strength engages fast-twitch muscle fibers (type II). Exogenous testosterone produces hypertrophy of both slow- and fast-twitch muscle fibers; nevertheless, it improves slow-twitch fibers more than fast-twitch fibers in males, as reported in previous studies[34,35].

Although there was no statistically significant association between insulin use and the two groups, the percentage of participants using insulin was numerically higher in the sarcopenic group than in those not using insulin (46.4% vs 29.1%, respectively) (Table 1, Supplementary Figure 4). From our collected data, the median duration of diabetes (in months) was 120 vs 60 ($p < 0.001$) (Supplementary Table 1), higher in participants using insulin compared to the insulin non-user group. Thus, the role of insulin use in sarcopenia cannot be addressed here. Moreover, previous studies have supported the notion that the effect of exogenous insulin on improving muscle strength is blunted with age and endogenous resistance[36].

The strengths of our study were the assessment of fibrosis by VCTE (rather than equation-based), dietary protein, physical activity level, and sleep duration, which were treated as study variables that could be potential confounders in assessing muscle mass and function. These findings reflect the need for muscle strength and mass assessment in individuals with liver fibrosis due to MASLD (diabetes) in daily practice, given the limited real-world studies and a gross lack of Indian data. Early diagnosis of sarcopenia is essential, as appropriate interventions in the form of diet, physical activities, adequate glycemic control, and evidence-based medications may prevent complications related to loss of muscle power and mass in males.

The major limitation of our study is the cross-sectional design in a single centre. As we had a secondary objective to assess the role of testosterone in muscle mass and function in that specific male population, we did not include female participants in the present study; therefore, the findings are not applicable to them. Furthermore, the interview-based recall method may yield inaccurate estimates of dietary protein intake and subjective measurements of daily physical activity duration. We found that the weekly protein intake was lower than the recommended daily intake; thus, further studies with appropriate dietary interventions and objective measurement of physical activity using an accelerometer are needed to eliminate biases and control for confounders. Although sodium-glucose cotransporter-2 (SGLT2) inhibitors might affect liver steatosis and muscle mass, they could not be excluded or discontinued during the study for ethical reasons (no participants were using GLP1 agonists). Moreover, DXA could be a better modality for ASM assessment, but we were limited to BIA due to availability constraints. Also, measurement of total testosterone can be erroneous in the background of liver fibrosis due to altered sex hormone binding globulin (SHBG), and free testosterone measurement could be better in terms of active androgen levels, which affects the muscle mass and power; however, we could not proceed for that due to the non-availability of equilibrium dialysis or liquid chromatography with mass spectrometry (LCMS/MS). Vitamin D deficiency is known to affect muscle mass and function, and could be a confounder not accounted for in the study. Future prospective studies, including females and excluding other potential confounders, may focus more on the precise relationship between liver fibrosis and sarcopenia and evaluate any gender-based differences in muscle mass and power associated with liver stiffness.

Despite that, we can conclude from this study that almost 1 out of 3 individuals with liver fibrosis in type 2 diabetes may suffer from sarcopenia, especially with longer duration of uncontrolled hyperglycemia. Persons with lower body weight and higher grades of liver fibrosis are more prone to develop sarcopenia in type 2 diabetes. The effects of insulin use and endogenous testosterone on muscle mass and function in liver fibrosis associated with type 2 diabetes are inconclusive in this study.

Ethics approval

The study was approved by the Institutional Ethics Committee (ECR/609/Instt/WB/2014/RR-20 issued under New Drugs and Clinical Trials Rules 2019 by the Drugs Controller General of India) of Nil Ratan Sircar Medical College and Hospital, Kolkata, India (IEC number – NRSMC/IEC/215/2023 dated 10th July 2023). It was conducted in adherence to the Declaration of Helsinki 1964 and its later amendments.

Consent to participate

Written informed consent was obtained from all study participants after the study process was explained.

Authors' contributions

Rajdeep Basu: Writing – original draft, Data curation, Formal analysis. Soumik Goswami: Conceptualization, Writing – review & editing. Nilanjan Sengupta: Conceptualization, Project administration, Writing – review & editing. Kumar Swapnil: Methodology. Arjun Baidya: Supervision. Sunetra Mondal: Supervision, Data curation. Soumita Mandal: Supervision, Data curation. Joydip Datta: Investigation. All authors read and approved the final version of the manuscript.

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Supplementary Material

Sample size calculation

The sample size for the proposed study was calculated using the formula for comparing two proportions[37].

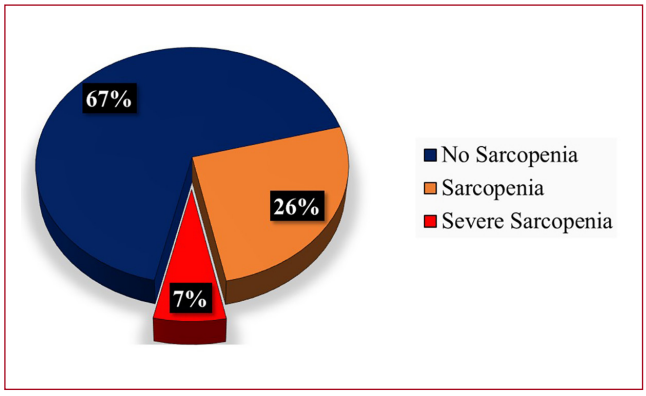
$$n = z^2 (p \times q)/e^2$$

where n = the sample size for the proposed study, Z = Standard error associated with the level of confidence (i.e., 1.96, two-tailed at 95% confidence interval), p = Prevalence or proportion of male participants with liver fibrosis in Type 2 diabetes mellitus sustaining the outcome of interest (i.e., sarcopenia), q = Complement of p, i.e., (100 − p), e = Allowable error around the reported prevalence; here it is assumed to be 8% (absolute).

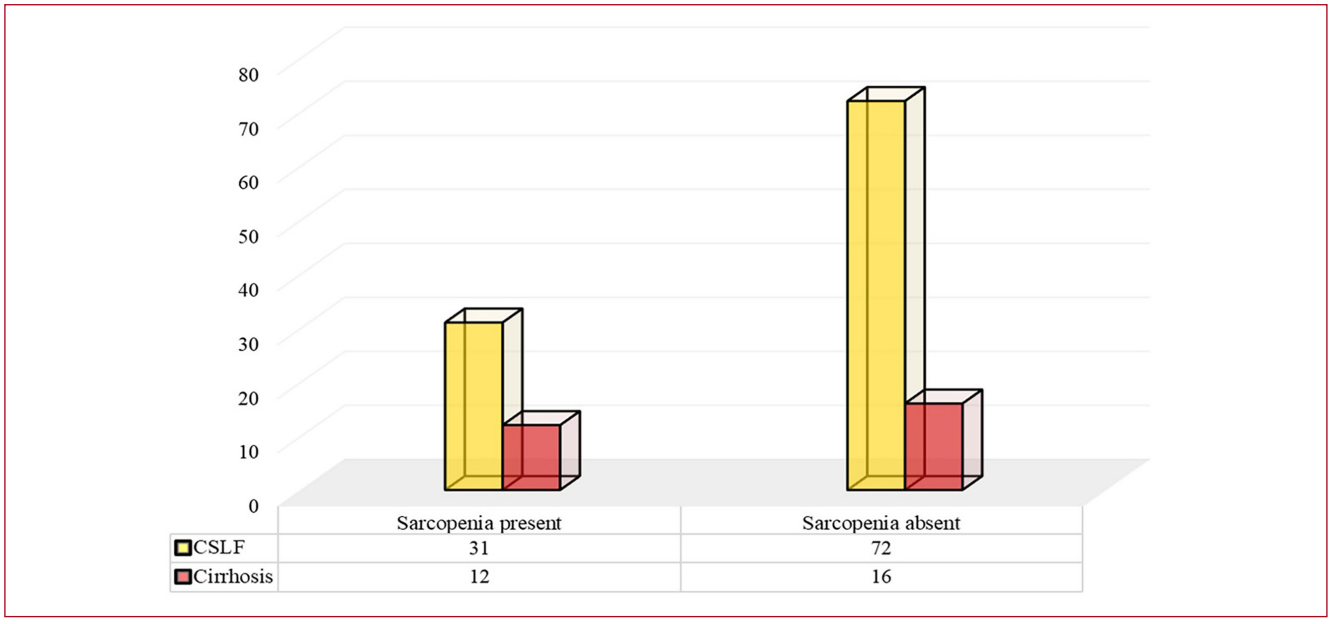
The prevalence of sarcopenia in liver fibrosis in Type 2 diabetic Asian males is 29%[38], as seen in the previous study. Thus, calculating the sample size based on the prevalence and also keeping available time & logistics in mind, it would be (n = 123) by the above formula. Now, assuming a 5% nonresponse rate, the revised sample size was [123 + 5% of 123] = 129.

Variables	Not using insulin (N = 103, 78.6%)	Using insulin (N = 28, 21.4%)	p-value
Age [years] (Median, IQR)	52 (45 – 60)	57 (50.8 – 60)	0.19§
Duration of diabetes [months] (Median, IQR)	60 (24 – 120)	120 (93 – 216)	<0.001§
HbA1c [%] (Median, IQR)	8.1 (7.4 – 9.1)	9 (7.6 – 10.2)	0.07§
LSM score [kPa] (Median, IQR)	10.2 (9 – 12.7)	9.7 (8.7 – 10.8)	0.11§

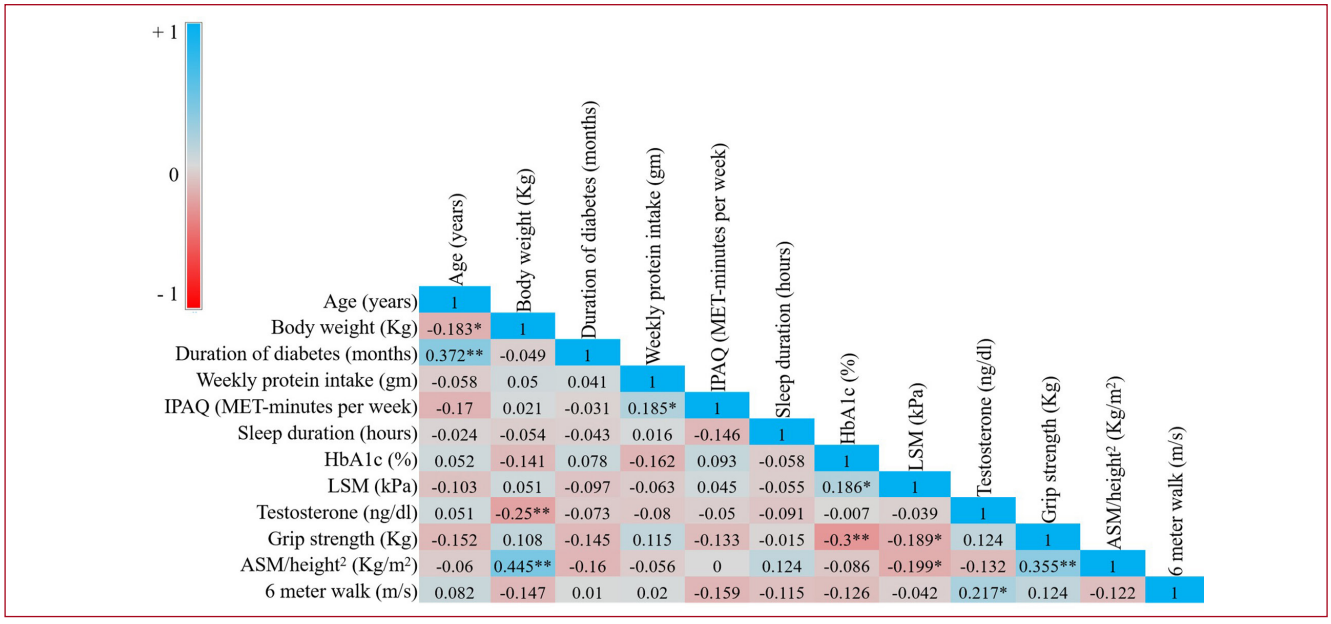
Supplementary Table 1. The median and interquartile range (IQR) of independent variables for participants using insulin with oral anti-diabetic agents and only oral anti-diabetic agents without insulin, HbA1c – Glycated hemoglobin, kPa – Kilopascal, LSM – Liver Stiffness Measurement, N – Number. § Mann-Whitney U test.



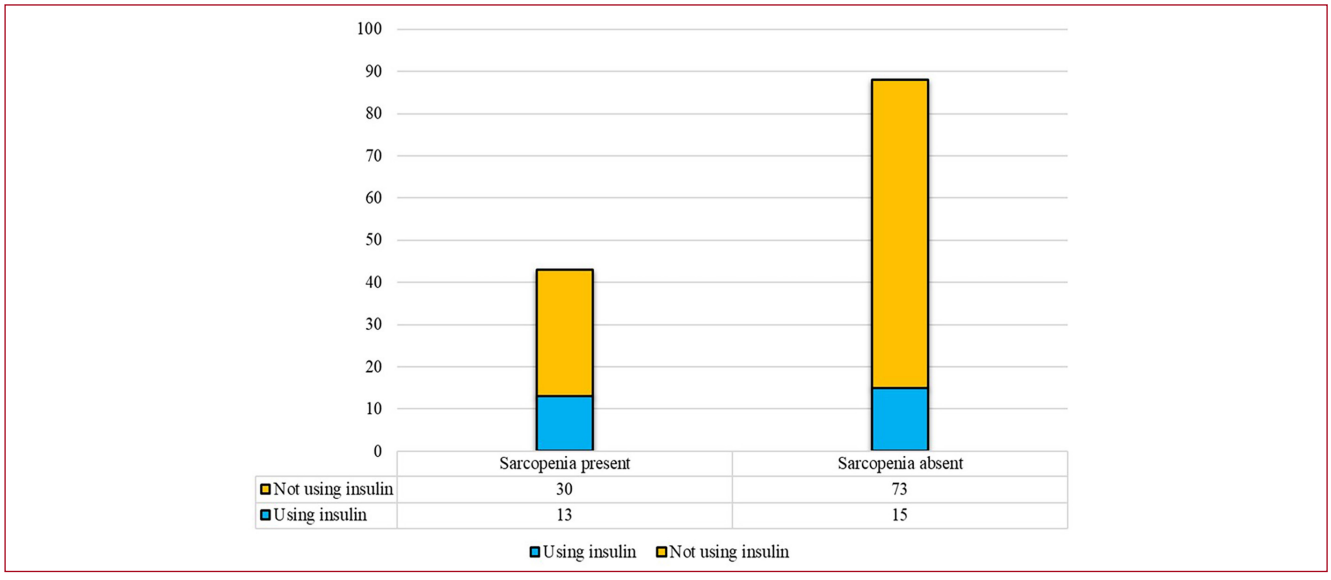
Supplementary Figure 1. Prevalence of severe sarcopenia in the study group.



Supplementary Figure 2. Prevalence of sarcopenia in the CSLF and Cirrhosis groups, CSLF – Clinically Significant Liver Fibrosis.



Supplementary Figure 3. Heatmap correlation matrix among continuous variables; cell values are suggestive of the Pearson coefficients (r). *p <0.05 **p <0.001. ASM – Appendicular Skeletal Mass, IPAQ – International Physical Activity Questionnaire, HbA1c – Glycated hemoglobin, kPa – Kilopascal, LSM – Liver Stiffness Measurement, MET – Metabolic Equivalent.



Supplementary Figure 4. Proportion of the use of insulin in sarcopenic and non-sarcopenic groups.