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Research Article

LIFESTYLE-RELATED PREDICTORS OF TESTOSTERONE DEFICIENCY AMONG MALE PATIENTS WITH CHRONIC SPINAL CORD INJURY

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ABSTRACT

Objectives: In the current study, the author evaluated the prevalence of low testosterone and its independent predictors among male patients with chronic spinal cord injury (SCI).

This descriptive type of observational study was conducted in the department of PMR at SMS Medical College.

Methods: In this cross-sectional study, 120 patients with chronic SCI were recruited, serum testosterone levels were assessed, and testosterone levels below 300 ng/dL were considered low. The following eight suspected independent predictors for low testosterone levels were assessed: age, body mass index (BMI), nicotine users, total lipid profile, level of injury, American Spinal Injury Association (ASIA) impairment scale, leisure-time physical activity (LTPA) score (h/week) via LTPA questionnaire, and aging male's symptom (AMS) score via AMS questionnaire.

Results: The mean age of the patients was 33.2±7.8 years. Patients with low testosterone exhibited a significant association with dorsal SCI (70.9%), motor complete (ASIA A and B) SCI (76.4%), nicotine use (65.5%), a higher triglyceride (TG) level (168.5 mg/dL), a higher total lipid level (712.9 mg/dL), and a higher AMS score (35.7). Patients with low testosterone were found to be engaged in lower (9.4 h/week) LTPA. A significant negative correlation of total testosterone levels was observed with TG ($r=-0.184$, $p=0.044$), total lipid ($r=-0.570$, $p<0.001$), BMI ($r=-0.504$, $p<0.001$), and AMS scores ($r=-0.549$, $p<0.001$). Whereas there was a significant positive correlation observed between total testosterone and LTPA ($r=0.380$, $p<0.001$).

Conclusion: The prevalence of low testosterone is found at 45.8%, and BMI, LPTA, AMS, and total lipids are identified as independent predictors of low testosterone.

Keywords: Chronic spinal cord injury, Low testosterone, Independent predictors, Leisure-time physical activity score, Aging male's symptom score.

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INTRODUCTION

Spinal cord injury (SCI) is one of the most common disabling conditions in India, and its high treatment cost along with a prolonged recovery period have a great burden on the patient and their family as well as on society. The common complications associated with SCI are cardiovascular, musculoskeletal, urological, endocrine complications, etc. Previous literature reported that SCI injury results in changes in body composition and metabolic profile, which result in accelerated aging and a decline in serum testosterone levels [1,2].

Testosterone in men is responsible for increased muscle mass, bone mineral density, and musculoskeletal strength. A literature review has shown that following SCI, there is a decrease in serum testosterone levels in men with acute as well as chronic SCI. Low levels of testosterone in this population result in decreased bone mineral density and muscle mass. The decrease in testosterone levels in SCI patients results in sexual dysfunction, reproductive dysfunction, and psychological and mental disorders as well [2,3]. The pathophysiology of testosterone deficiency in men with SCI is still not clearly understood. Recent studies suggest that decreased physical activity, comorbidities, a decrease in sexual thoughts, weakened morning erections, erectile dysfunction, poly-medications, and obesity are commonly associated with SCI, which may result in a decreased serum testosterone level in SCI patients [2].

Androgen deficiency is a treatable co-morbidity, so to prevent the complications associated with low testosterone, it has become important to identify androgen deficiency as early as possible in the SCI population [4]. Testosterone hormone has an important role in quality of life, but its screening is still not part of the standard medical care for men with SCI. Previous literature has shown that low sexual desire, decreased physical activity, a higher body mass index (BMI), lower insulin sensitivity, and erectile dysfunction are independently associated with low testosterone levels in men with SCI [5]. Some of these factors are modifiable predictors, so identification of these modifiable independent predictors of low testosterone levels would be helpful in better managing the complications associated with low testosterone levels in men with chronic SCI by promoting lifestyle modifications. The purpose of the current study was to find out the prevalence of low total testosterone and independent predictors of low testosterone levels among male patients with chronic SCI.

Objectives

The objectives of this cross-sectional study were to find out the prevalence of low testosterone among chronic SCI patients and to find out the independent predictors of low testosterone levels among male patients with chronic SCI by correlating various socio-demographic, clinical, and laboratory variables with testosterone levels.

METHODS

Study population

This cross-sectional study was conducted in a tertiary care hospital (SMS Hospital) in Jaipur, Rajasthan, from October 2020 to November 2021. Male patients between the age group of 20 and 50 years with neurologically stable chronic (>1 year) traumatic SCI were recruited in this study. Patients of SCI, with a history of testosterone replacement therapy, any acute medical or surgical illness, complete quadriplegia, or

any type of communication or cognitive disorder were excluded from the study.

The institute's ethics committee's approval was obtained, and the study was registered in the Clinical Trials Registry-India (CTRI/2020/10/028367). A total of 120 patients with chronic SCI who satisfied the study inclusion criteria were recruited for the present study, and informed written consent was obtained from all the participants.

The sample size of 120 chronic SCI patients was taken with a study power of 80% and an alpha error of 0.05, assuming a 33% prevalence of low testosterone levels among men with chronic SCI and eight suspected independent predictors of low testosterone as found in the seed article by Barbonetti *et al*. 2014 [5].

Neurological assessment

A detailed neurological assessment was done, and the American Spinal Injury Association (ASIA) protocol was used to define both the level and completeness of the lesion [6]. Patients with complete lesions with no sensory or motor function preserved in the lowest sacral segment were categorized as A, whereas patients with incomplete lesions were categorized as B–D as per the ASIA protocol.

Outcome measures

Following eight suspected independent predictors of low testosterone level in chronic SCI patients were assessed: age, BMI, nicotine users, total lipid profile, level of injury, ASIA impairment scale, leisure-time physical activity (LTPA) score (h/week) via LTPA questionnaire, and aging male's symptom (AMS) score by AMS questionnaire.

Age, nicotine use, total lipid, triglyceride (TG), level of injury, LTPA score, and AMS score were recorded in a pre-designed performa.

1. Anthropometric measures: Weight was taken using a professional mechanical chair scale. Height was determined by a measuring tape. The BMI was calculated in kilograms per square meter (kg/m^2) as per BMI guidelines by the WHO
2. Assessment of hypogonadism-related symptoms: All the participants were asked to complete the AMS questionnaire to determine subjective symptoms of clinical hypogonadism. The AMS consists of 17 questions, which were further divided into psychological (questions 6–8, 11 and 13), somato-vegetative (questions 1–5, 9 and 10), and sexual (questions 12 and 14–17) sub-scales
3. Assessment of LTPA: LTPA includes the activities that are performed during your free time. In the present study, we used the LTPA questionnaire for people with SCI (LTPAQ-SCI) to assess LTPA. The number of days during which LTPA was performed in the last 7 days was recorded, and then the patients were asked to recall the minutes per day they spent in LTPA. The final score was obtained by multiplying the number of days per week by the number of minutes per day for LTPA. Total weekly minutes were divided by 60 to obtain the number of hours of activity performed over the past week.
4. Hormones and biochemistry: A morning fasting venous blood sample was collected from each subject between 08:00 and 09.00 am, and serum testosterone level was measured by ADVIA Centaur XP by chemiluminescence immunoassay method. Serum total lipids and TG were also assessed from the sample. A total testosterone level below 300 ng/dL was considered low testosterone level, as suggested by endocrine society guidelines [7].

Statistical analysis

The data thus collected were recorded in a pre-designed performa, entered into a computer Excel sheet to prepare a master chart, and then analyzed. Categorical/nominal variables were summarized as numbers and/or percentages and analyzed using the Chi-square test or Fisher's exact test, as applicable. Continuous variables were summarized as mean and standard deviation, as well as median and range, and were analyzed using an independent sample t-test for comparison between the two groups. The correlation between two continuous variables was assessed using the Pearson correlation coefficient. A linear regression analysis was done to determine the independent predictors associated with testosterone levels. A $p<0.05$ was taken as statistically significant. Receiver operating characteristics analysis over weekly LTPA (h/week) was used to determine whether threshold levels could be found to provide an accurate discriminating ability in predicting low total testosterone levels.

RESULTS

The mean age of patients was 33.2±7.8 years. The characteristics of the study population are shown in Table 1. The mean BMI of the study population was 23.9±1.8, 48.3% of participants were nicotine users, and 60.8% of patients had injury durations between 1 and 2 years. Seventy (58.3%) patients had dorsal spine injuries, and 62 (51.7%) patients had ASIA grade A injuries. On blood sample evaluation, 55 (45.8%) patients had low testosterone levels (<300 ng/dL) and 65 (54.2%) patients had normal testosterone levels (>300 ng/dL). The current study observed that the prevalence of low testosterone in SCI patients is 45.8%.

The study observed no significant relationship between the age of the SCI patients and testosterone level (p=0.270). Patients with low testosterone exhibited a significant association with dorsal SCI (70.9%, p=0.011), motor complete (ASIA-A and B) SCI (76.4%, p=0.005), and nicotine use (65.5%, p=0.001). Significantly higher TG levels (168.5±54 mg/dL, p=0.001), total lipid levels (712.9±120.2 mg/dL, p≤0.001), BMI (24.8±1.8 kg/m^2, p≤0.001), and AMS questionnaire scores (35.7±4.4, p≤0.001) were seen in patients with testosterone deficiency. Patients with low testosterone were found to be engaged in lower (9.4±3.2 h/week, p≤0.001) LTPA (Tables 2 and 3).

When the study variables were compared with the testosterone level, results revealed that there was no significant correlation between

Table 1: Demographic and characteristics of the study population

Characteristics	Frequency
Age (years) Mean±SD	33.2±7.8
Testosterone level, (n, %)	
<300 ng/dL	55, (45.8)
≥300 ng/dL	65, (54.2)
Marital status (n, %)	
Married	103, (85.8)
Unmarried	17, (14.2)
BMI (n, %)	
<18 kg/m^2	1, (8)
18–25 kg/m^2	83, (69.2)
>25 kg/m^2	36, (30)
Nicotine use, (n, %)	
Yes	58, (48.3)
No	62, (51.7)
Duration of injury (n, %)	
Years	73 (60.8)
>2 years	47 (39.2)
Level of injury (n, %)	
Intact	18, (15)
Cervical	6, (5)
Dorsal	70, (58.3)
Lumber	26, (21.7)
ASIA grade (n, %)	
ASIA - A	62, (51.7)
ASIA - B	11, (9.2)
ASIA - C	23, (19.2)
ASIA -D	6, (5)
ASIA - E	18, (15)
Total lipids (n, %)	
≤750 mg/dL	88, (73.3)
>750 mg/dL	32, (26.7)
Triglyceride level (n, %)	
≤165 mg/dL	67, (55.8)
>165 mg/dL	53, (44.2)

Table 2: Relation of study variables with test osterone level

Variables	Testosterone ≤300 ng/dL		Testosterone ≥300 ng/dL		p-value
	n	%	n	%	
Age group (years)					
20–29	20	36.4	26	40.0	p=0.270 (NS)
30–39	19	34.5	28	43.1	
40-50	16	29.1	11	16.9	
Nicotineuse					
Yes	36	65.5	22	33.8	0.001 (S)
No	19	34.5	43	66.2	
Level of injury					
Cervical	3	5.5	3	4.6	0.011 (S)
Thoracic	39	70.9	31	47.7	
Lumbar	11	20.0	15	23.1	
Intact	2	3.6	16	24.6	
ASIA grade					
A	36	65.5	26	40.0	0.005 (S)
B	6	10.9	5	7.7	
C	10	18.2	13	20.0	
D	1	1.8	5	7.7	
E	2	3.6	16	24.6	
LTPA					
Mild	43	78.2	6	9.2	<0.001 (S)
Moderate	12	21.8	51	78.5	
Heavy	0	0	8	12.3	

Table 3: Relationofmeans of study variableswithtestosteronelevel

Variables	Testosterone <300 ng/dL	Testosterone ≥300 ng/dL	p-value
BMI Kg/m^2	24.8±1.8	23.2±1.3	<0.001 (S)
LTPA hour/week	9.4±3.2	13.2±3.7	<0.001 (S)
TG level in mg/dL	168.5±54	134.8±52.1	0.001 (S)
Total lipid level (mg/dL)	712.9±120.2	548.9±103.6	<0.001 (S)
AMSs core	35.7±4.4	31.7±5.3	<0.001 (S)
AMS psychological score	11.02±1.62	9.23±1.64	<0.001 (S)
AMS somatic score	14.74±1.88	12.48±2.54	<0.001 (S)
AMS sexual score	12.91±2.08	9.97±2.11	<0.001 (S)
Sexual desire item	3.11±0.60	1.66±0.54	<0.001 (S)

the age of the patient and the testosterone level (r=−0.151, p=0.098). A significant negative correlation of total testosterone levels was observed with TG (r=−0.184, p=0.044), total lipid (r=−0.570, p<0.001), BMI (r=−0.504, p<0.001), and AMS scores (r=−0.549, p<0.001). Whereas there was a significant positive correlation between total testosterone and LTPA (r=0.380, p<0.001). We observed that there was a significant negative correlation of total testosterone level with AMS sub-scores, sexual score (r=−0.572, p<0.001), and sexual desire item score (r=−0.779, p<0.001). Psychological score (r=−0.408, p<0.001) and somato-vegetative score (r=−0.439, p<0.001) had shown a moderately negative correlation with testosterone level (Table 4 and Figs. 1 and 2).

At ROC analysis, less than 8.5 h/week of LTPA discriminated patients with Testosterone deficiency with a sensitivity of 61.8% and specificity of 84.6% (AUC: 0.76; 95% CI: 0.68–0.85) (Fig. 3a). A BMI ≥24.99 kg/m^2 discriminated patients with testosterone deficiency with a sensitivity of 56.4% and specificity of 92.3% (AUC:0.78; 95% CI: 0.69–0.86) (Fig. 3b).

The results from linear regression analysis with a 95% confidence interval of the association of total testosterone with its independent predictors are summarized in Table 5. We observed that BMI, LPTA, AMS, and total lipids are independent predictors of low testosterone levels in SCI patients. Whereas age, TG level, nicotine use, level of injury, and ASIA grade were not independent predictors of low testosterone in these populations.

Table 4: Correlation of test osterone level with study variable

Parameter	Correlationcoefficient	p-value
Age	−0.151	0.098 (NS)
TG	−0.184 (weak negative correlation)	0.044 (S)
Totallipid	−0.570 (moderate negative correlation)	<0.001 (S)
BMI	−0.504 (moderate negative correlation)	<0.001 (S)
LTPA	0.380 (weak positive correlation)	<0.001 (S)
AMS		
Total	−0.549(moderate negative correlation)	<0.001 (S)
Psychologicalscore	−0.408 (moderate negative correlation)	<0.001 (S)
Somatic score	−0.439 (moderate negative correlation)	<0.001 (S)
Sexualscore	−0.572 (Strong negative correlation)	<0.001 (S)
Sexualdesireitemscore	−0.779 (Strong negative correlation)	<0.001 (S)

TG: Triglyceride

Table 5: Independent predictors associated with low test oster one level

Parameters	B coefficient	95.0% confidence interval for B		p-value
		Lower bound	Upper bound	
Age	0.185	−2.263	2.634	0.881
ASIA grade	6.950	−12.251	26.151	0.475
Level of injury	−32.307	−67.038	2.424	0.068
Nicotine user	−23.629	−64.349	17.092	0.253
Triglyceride	0.294	−0.111	0.698	0.153
Total lipids	−0.358	−0.561	−0.154	0.001
BMI	−19.109	−31.588	−6.631	0.003
LTPA	6.475	1.659	11.291	0.009
AMS	−8.08	−11.54	−4.62	0.001

LTPA: Leisure-time physical activity

The results from linear regression models exploring independent predictors associated with low testosterone levels are summarized in Table 6. A lower level of total testosterone was associated with higher total AMS scores and higher psychological, somato-vegetative, sexual, and sexual desire item sub-scores of the AMS questionnaire. However, after BMI, age, and weekly LTPA adjustment, the associations of lower total testosterone were more significant with higher sexual desire item sub-score of the AMS questionnaire than other AMS sub-scores.

DISCUSSION

In our study, we observed that male patients with chronic SCI had low testosterone levels, and the prevalence of low testosterone was reported as 45.8%. Previous studies also observed similar findings [8, 9]. The predictors of low testosterone in SCI are still a matter of research for rehabilitation physicians, and in the present study, we identified that BMI, LPTA, AMS, and total lipids are the independent predictors of low testosterone levels in chronic SCI patients. Most of these predictors identified in the current study are modifiable, so lifestyle modification could be helpful in the management of testosterone deficiency in SCI patients.

In the present study, we observed that BMI is an independent predictor of low testosterone levels and that it has a significant independent association with the level of testosterone, explaining 19.9% of its variability. Previous studies also reported that BMI is an independent predictor of low testosterone in SCI patients [2, 5, 10]. Obesity is a

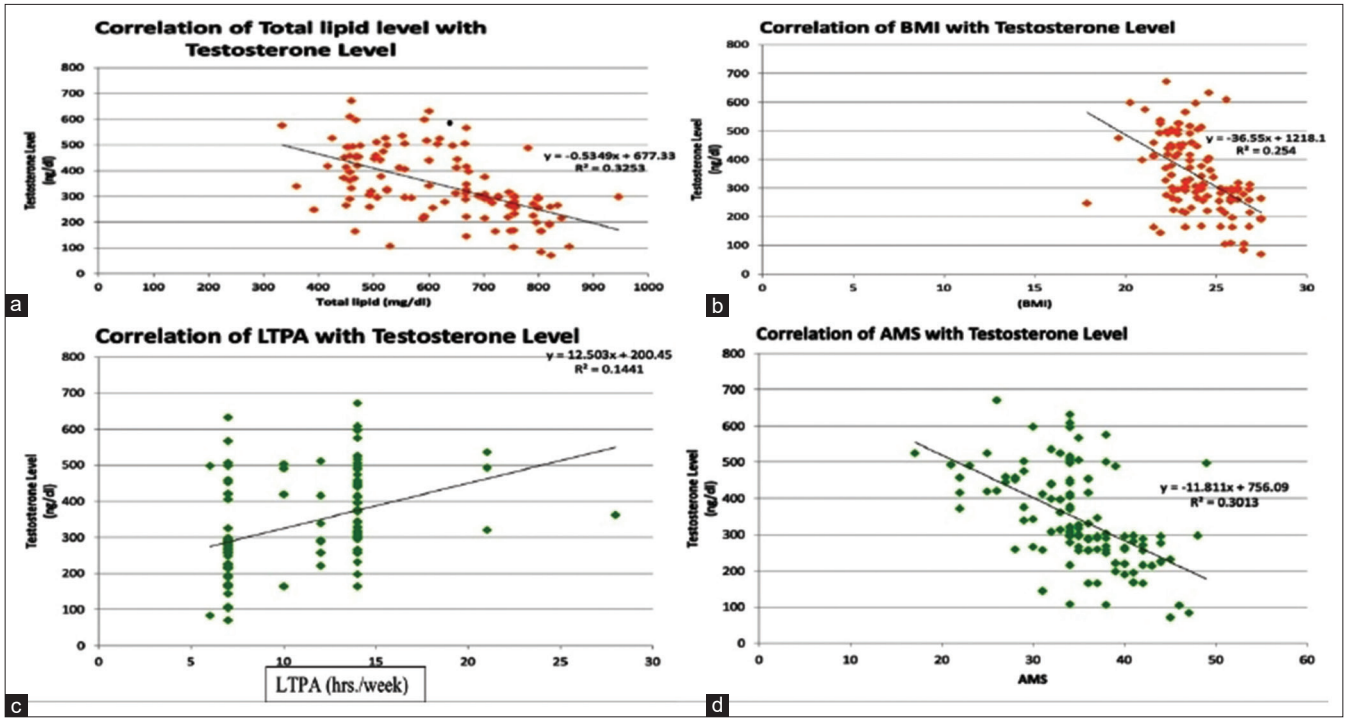

Fig. 1: (a) Correlations between total lipid and test osterone, R^2=0.3253, (b) Relationship between BMI and test osterone, R^2=0.1441, (c) Relationship between LTPA and test osterone, R^2=0.254, (d) Relationship between AMS and test osterone, R^2=0.3013

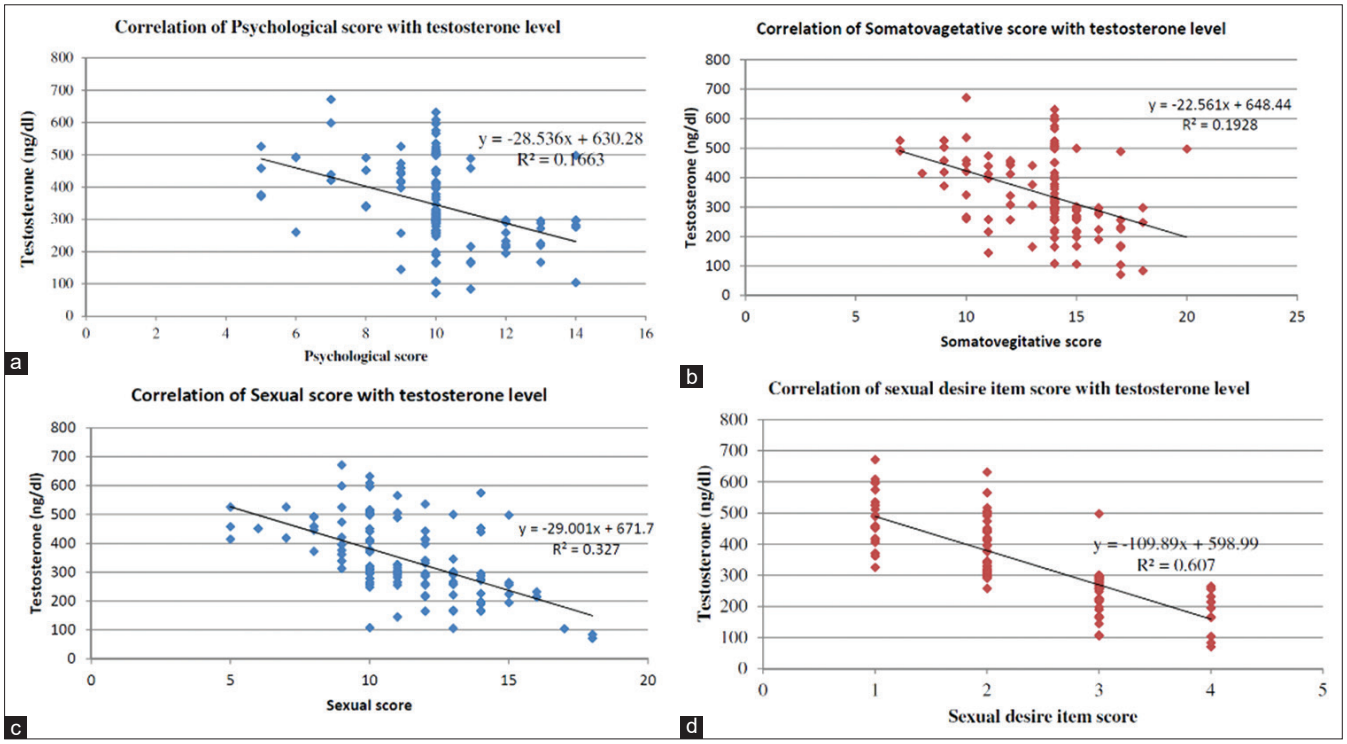

Fig. 2: Correlations of AMS Sub Score (a) Psychological, (b) Somatic, (c) Sexual and (d) Sexual desire item score with testosterone level

common comorbidity observed following SCI, which is attributed to low testosterone levels, so lifestyle modification in these patients reduces the risk of obesity-related or low testosterone-related complications [11, 12]. Gater DR observed in his study that SCI patients have around 15% more body fat as compared to BMI-matched abled persons [13]. In patients with SCI, obesity or high body fat is mostly because of a sudden decrease in their physical activity or lack of neuronal stimulation, resulting in a loss of muscle or bone mass and an increase in body fat [14]. So, lifestyle modification may increase the testosterone level in this population and reduce the complications related to low testosterone.

We observed that the level of physical activity (LTPA) has an independent association with the level of testosterone, explaining 13.3% of its variability. We observed that SCI patients who were involved in a longer duration of LTPA (>13.2±3.7 h/week) with a BMI <25 kg/m^2 had ≥300 ng/dL serum testosterone level, which is a similar finding

Table 6: Independent predictors associated with low test osterone level

Variables	β-coefficient	AdjustedforBMI	Model III: adjusted forBMI, age	Model IV: adjusted for BMI, age, and LTPA
TG	−0.429 (−0.848, −0.010) p=0.045	−0.194 (−0.57, 0.182) p=0.308	−0.193 (−0.572, 0.187) p=0.317	−0.151 (−0.512, 0.210) p=0.408
AMS	−11.81 (−15.09, −8.53) p<0.001	−9.04 (−12.3, −5.77) p<0.001	−9.39 (−12.74, −6.04) p<0.001	−8.08 (−11.54, −4.62) p<0.001
AMS psychological sub-score	−28.54 (−40.18, −16.9) p<0.001	−20.67 (−31.5, −9.9) p<0.001	−22.19 (−33.5, −10.87) p<0.001	−17.49 (−28.95, −6.02) p=0.003
AMS Somato-vegetative sub-score	−22.56 (−30.98, −14.15), p<0.001	−15.94 (−24.0, −7.89) p<0.001	−16.39 (−24.62, −8.16) p<0.001	−13.06 (−21.38, −4.75) p=0.002
AMS sexual score	−29.0 (−36.59, −21.42) p<0.001	−22.54 (−30.16, −14.91) p<0.001	−22.55 (−30.23, −14.88) p<0.001	−20.03 (−27.69, −12.36) p<0.001
AMS sexual desire item score	−109.9 (−126, −93.8) p<0.001	−98.5 (−116.5, −80.5) p<0.001	−98.5 (−116.6, −80.5) p<0.001	−94.7 (−114.1, −75.2) p<0.001

AMS: Aging male's symptom, TG: Triglyceride, LTPA: Leisure-time physical activity

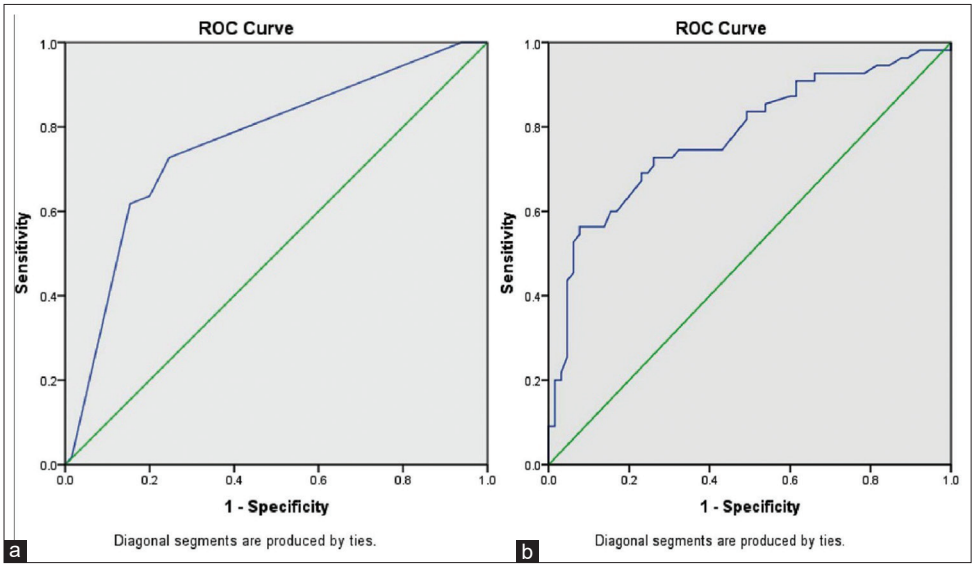

Fig. 3: (a) On ROC analysis, <8.5 h/week of LTPA distinguished patients withtestosterone deficiency with a sensitivity of 61.8% and specificity of 84.6% (AUC: 0.76; 95% CI: 0.68–0.85), (b) On ROC analysis, BMI >24.99 kg/m^2 distinguished patients with testosterone deficiency with a sensitivity of 56.4% and specificity of 92.3% (AUC: 0.78; 95%CI: 0.69–0.86)

observed by Barbonetti *et al*. [5]. Rosety-Rodriguez *et al*. also observed that chronic SCI patients who performed exercises (arm crank exercises) had high testosterone levels as compared to those who did not perform [15]. Previous literature also supported that, in addition to routine activities, patients with SCI should also perform leisure activities to maintain testosterone levels and improve subjective wellbeing, and this would also decrease the risk of heart disease, diabetes, and obesity [16-19]. Both high BMI/obesity and low leisure activities are modifiable risk factors. High BMI and low LTPA are independent predictors of low testosterone levels, so modification of these factors can be utilized in the treatment of testosterone deficiency in men with SCI [20].

This study observed that total lipid level is an independent predictor of low testosterone level and showed an independent association with the level of testosterone, explaining 8.7% of its variability, but we did not observe such an association with serum TG levels in linear regression analysis. Similar to our findings, Abilmona *et al*. and Barbonetti *et al*. also reported that total lipid concentration level is an independent predictor of low testosterone levels in chronic SCI patients [5, 10]. Based on this study and literature review, we concluded that testosterone replacement therapy can be considered for improving lipid levels in patients with chronic SCI [21].

We observed that higher AMS scores and sub-scores (psychological, somato-vegetative, sexual, and sexual desire items) are significantly associated with low testosterone levels in SCI patients, and during linear regression analysis, it was observed that AMS was an independent predictor of low testosterone. Similar to our findings, Wu *et al*. also observed that poor sexual desire was independently associated with lower testosterone levels [22].

Similar to previous studies, we also observed that there was no significant correlation of testosterone level with age and duration of injury in SCI patients [8, 9, 22, 23]. Although in the current study we observed that low serum testosterone levels were more prevalent in the >40-year-old of age group as compared to younger patients with SCI, but it was not statistically significant. This finding is similar to those observed by Bauman *et al*. [2]. Thus, we believe that the high prevalence of normal testosterone levels in the current study may be due to the low mean age of our study population and a high prevalence of moderate LTPA.

We observed that SCI patients who were smoking had low testosterone levels as compared to non-smokers; however, we also observed that smoking was not an independent predictor of testosterone levels. Behnaz *et al*. also observed that smoking was not an independent predictor of testosterone level [24].

Limitations

The primary limitation of our study was the study design. This study was a transverse (cross-sectional) study, but only longitudinal intervention

studies could establish better cause-and-effect relationships. Another limitation is that we use BMI as a measure of body fat, but we consider that percentage of body fat could be a better predictor of testosterone deficiency in SCI patients as compared to BMI, as reported by previous studies [25, 26].

CONCLUSION

We concluded that total lipid, LTPA, BMI and AMS were found to be independent predictors of low testosterone in chronic SCI patients. The main predictors of low testosterone (total lipid, LTPA, and BMI) are lifestyle-related modifiable, and further studies could explore the possible effects of lifestyle modification on increasing testosterone levels and improving low sexual desire in men with chronic SCI. We also concluded that lifestyle modification is a safe and effective method as compared to testosterone replacement therapy to treat the complications related to low testosterone in patients with SCI.

Clinical relevance

1. Serum testosterone level and all suspected predictors should be assessed as the routine protocol in rehabilitation services because this could be helpful in the development of guidelines for testosterone testing/monitoring, and replacement therapy, which could enhance the rehabilitation outcome for SCI
2. Education regarding lifestyle modification could be helpful to prevent complications from low testosterone in the SCI population.

AUTHORS CONTRIBUTION

All the authors contributed equally to the concept of the article, in data collection, interpretation of data, and manuscript preparation.

CONFLICT OF INTEREST

None.

AUTHORS FUNDING

Nil.

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