

ORIGINAL ARTICLE

# Prevalence of androgen deficiency in chronic spinal cord injury patients suffering from erectile dysfunction

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**Study design:** Retrospective cross-sectional study.

**Objectives:** To estimate the prevalence of biochemical androgen deficiency in Iranian spinal cord injured men suffering from erectile dysfunction (ED) and to determine factors related to this problem.

**Setting:** An andrology clinic of a teaching hospital in Tehran.

**Methods:** Men, 18 years of age and older, with chronic (>2 years) spinal cord injury (SCI) suffering from ED were recruited. Demographic data, hormonal and lipid levels, injury variables and drug history were obtained from the medical records. The relationships between biochemical androgen deficiency (unequivocally low serum testosterone levels) and patient characteristics, injury variables and laboratory data were determined.

**Results:** Out of 319 patients, 32.6% had total testosterone deficiency and 29.1% had biochemical androgen deficiency. Of those with biochemical androgen deficiency, 93.5 and 85.7% had luteinizing hormone (LH) and follicle stimulating hormone (FSH) within or below the normal ranges, respectively. Opioid use, triglyceride (TG) and total cholesterol (TC) were associated with biochemical androgen deficiency. Significant correlations between total testosterone level and sex hormone binding globulin ( $r=0.3$ ,  $P<0.001$ ), LH ( $r=0.2$ ,  $P=0.02$ ), TC ( $r=-0.1$ ,  $P=0.04$ ) and TG ( $r=-0.3$ ,  $P<0.001$ ) were found.

**Conclusion:** A substantial proportion of our patients with chronic SCI and ED had biochemical androgen deficiency. Opioid use, TG and TC levels were associated with biochemical androgen deficiency in our studied population. Standard screening of androgen deficiency and testosterone replacement therapy are recommended in men with chronic SCI suffering from ED.

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## INTRODUCTION

Spinal cord injury (SCI) is related to variety of problems in human body systems. Previous studies have shown high prevalence of cardiovascular, musculoskeletal, urological, reproductive and endocrine complications in patients suffering from SCI. Two of the most important concerns in spinal cord injured men are erectile dysfunction (ED) and alterations in the secretion of hormones such as testosterone and gonadotropins.<sup>1–4</sup> Testosterone as a principle male sex hormone has several important functions. Decline in serum testosterone concentration has negative effects on the body, from bone and muscle loss, to sexual and reproductive dysfunctions, to psychological and mental disorders.<sup>5,6</sup>

Androgen deficiency is a clinical syndrome with typical signs and symptoms and unequivocally low serum testosterone levels, according to the Endocrine Society clinical practice guidelines.<sup>7</sup> Common clinical features in men with SCI are similar to hypogonadal men. It suggests that these health problems could be attributed to androgen deficiency which may play a crucial role in the quality of life and well-being of SCI patients. Taken together, it seems that identification of androgen deficiency as a treatable co-morbidity is important in this population.<sup>1,8</sup>

In recent years, some studies have reported high prevalence of testosterone deficiency in men following SCI, while others have not found this abnormality. Given that acute physical distress and systemic diseases affect testosterone level,<sup>9</sup> high incidence of testosterone deficiency is expected following acute SCI. However, the effect of chronic SCI on serum testosterone level is still controversial. The reason may be lack of studies with adequate sample size and methodological concordance.<sup>10,11</sup>

In this study we aimed to determine the prevalence of biochemical androgen deficiency in a large population of Iranian men with chronic SCI suffering from ED. The secondary goal of this study was to investigate the relationship between this problem—biochemical androgen deficiency—and patient characteristics, injury variables and laboratory data.

## METHODS

This retrospective and cross-sectional study was carried out in Shafa Research Center, Khatam Al-Anbia hospital, Tehran, Iran from January 2013 to March 2015. The protocol was approved by the institutional review board and ethics committee. Three hundred nineteen men with established SCI attending an andrology clinic were recruited into the study. Men, 18 years of age and older,

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with chronic SCI (>2 years since injury) suffering from ED were included in our study. Patients were excluded if had prostate cancer, pituitary microadenoma, chronic liver or kidney disease, respiratory failure, coronary artery disease, history of traumatic genitalia injury and history of taking medications that may alter testosterone levels, including anabolic steroids, corticosteroids, finasteride, spironolactone, ketoconazole, digoxin, verapamil, carbamazepine, valproic acid and phenytoin. As our participants used low potency and short-acting opioid analgesics (for example, codeine and tramadol) on an as needed basis, we did not consider opioid use as an exclusion criterion.

Patient characteristics, date and neurologic level of injury, American Spinal Injury Association Impairment Scale (AIS) grade, drug history and laboratory values were obtained from the medical records. Laboratory values included total testosterone (TT), sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), triglyceride (TG), total cholesterol (TC) and albumin.

Neurological level and completeness of the lesion were defined by using International Standards for Neurological Classification of SCI.<sup>12</sup> Moreover, ED was evaluated by an andrologist according to physical examination and International Index of Erectile Function (IIEF).<sup>13</sup>

All blood samples were drawn in a fasting state between 0800 and 1000 hours, measured by the same laboratory. Total testosterone, LH, FSH and PRL were measured by enzyme-linked fluorometric assay technique according to the manufacturer's guidelines on the Tosoh AIA system analyzer (Tosoh Bioscience N.V., Tessenderlo, Belgium). The serum SHBG level was determined using enzyme-linked immunosorbent assay kit (IBL international, Hamburg, Germany). The lower limit of detection for testosterone, LH, FSH, PRL and SHBG was 0.2 nmol l<sup>-1</sup>, 0.2 IU l<sup>-1</sup>, 1.0 IU l<sup>-1</sup>, 44 pmol l<sup>-1</sup> and 0.77 nmol l<sup>-1</sup>, respectively. Triglyceride and TC were assessed by enzymatic photometric technique (kit: Parsazmun Company, Tehran, Iran). Serum albumin was measured by bromocresol green method using a commercial kit (Parsazmun Company).

According to Endocrine Society guidelines, biochemical androgen deficiency was defined as TT levels lower than 10.4 nmol l<sup>-1</sup>. Alternatively, FT levels <0.225 nmol l<sup>-1</sup> were used as a criteria for biochemical androgen deficiency in patients in whom TT levels were insufficient for diagnosis—patients with SHBG abnormality or TT levels near the lower limit of normal.<sup>7,14</sup> Vermeulen formula was used to calculate FT in these patients.<sup>15</sup> The formula is available on the ISSAM Web site ([www.issam.ch/freetesto.htm](http://www.issam.ch/freetesto.htm)).

High PRL levels were determined as stated in the Endocrine Society and Pituitary Society guidelines.<sup>16,17</sup> Interpretation of other laboratory data was based on manufactures' instruction. Reference ranges for SHBG, LH and FSH were 15–100 nmol l<sup>-1</sup>, 1.7–11.2 IU l<sup>-1</sup> and 2.1–18.6 IU l<sup>-1</sup>, respectively.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

### Statistical analysis

Statistical analysis was performed using SPSS software version 16.0. Normal distribution of continuous variables was assessed using Kolmogorov–Smirnov test. Continuous variables with normal distribution were described as mean and s.d. Variables with lack of normal distribution were expressed as median and interquartile range (IQR). The mean difference of normally distributed parameters in studied groups was assessed using independent sample *t*-test, while Mann–Whitney *U* test was used to analyze the significance of the difference between nonparametric variables. Categorical data were shown as number (percentage). Associations between categorical data and biochemical androgen deficiency were examined by using  $\chi^2$  analysis. Spearman's correlation test was performed to investigate the correlations. The association of demographic and clinical characteristics with risk of biochemical androgen deficiency was assessed using two models of logistic regression analysis. Model 1 was crude association between each independent variables and biochemical androgen deficiency (univariate model), whereas in Model 2 this association was adjusted for age, duration of SCI, level of injury, extent of injury, smoking and opioid usage (multivariate model). The results were described as odds ratio (OR) and 95% confidence interval (CI). A *P*-value <0.05 was considered statistically significant.

**Table 1 Sociodemographic and disease characteristics of participants in studied groups**

Variables	Biochemical androgen deficiency		P-value
	Yes (n = 93)	No (n = 226)	
Age (year) <sup>a</sup>	47.4 (6.7)	47.1 (7.8)	0.707
SCI duration (year) <sup>b</sup>	27.0 (25.0–29.0)	26.0 (24.0–29.0)	0.099
<i>Marital status<sup>c</sup></i>			
Married	89 (95.7)	213 (94.2)	0.869
Single	3 (3.2)	10 (4.4)	
Divorced	1 (1.1)	3 (1.3)	
<i>Smoking<sup>c</sup></i>			
Yes	31 (33.3)	55 (24.4)	0.105
No	62 (66.7)	170 (75.6)	
<i>Opioid use<sup>c</sup></i>			
Yes	16 (17.2)	21 (9.3)	0.045
No	77 (82.8)	205 (90.7)	
<i>Level of injury<sup>c</sup></i>			
Cervical	12 (13.0)	31 (13.8)	0.204
Thoracic	54 (58.7)	150 (67.0)	
Lumbosacral	26 (28.3)	43 (19.2)	
<i>Extent of injury<sup>c</sup></i>			
ASIA score A (complete)	45 (50.0)	124 (57.4)	0.235
ASIA score B–D (incomplete)	45 (50.0)	92 (42.6)	
<i>Wheelchair bound<sup>c</sup></i>			
Yes	69 (82.1)	191 (89.3)	0.098
No	15 (17.9)	23 (10.7)	

Abbreviations: ASIA, American spinal injury association; IQR, interquartile range; SCI, spinal cord injury.

<sup>a</sup>Age was expressed as mean (s.d.).

<sup>b</sup>Duration of SCI was expressed as median (IQR).

<sup>c</sup>Categorical variables were expressed as number (percentage).

### RESULTS

The mean (s.d.) age of our study population was 47.2 (7.5) years with range of 24–77 years. The median (IQR) duration of their SCI was 26.0 (24.0–29.0) years with range of 2–33 years. Biochemical androgen deficiency was confirmed in 93 patients (prevalence: 29.1%, 95% CI: 24.2–34.5). Low TT level was found in 104 patients (prevalence: 32.6%, 95% CI: 27.5–38.1). The median (IQR) of TT was 12.4 (9.0–16.5) nmol l<sup>-1</sup> in the studied population.

Sex hormone binding globulin level was low in 48 (15.0%) patients. None of the participants had high SHBG level. In participants with low SHBG levels, 26 (54.1%) had normal TT and FT levels, 13 (27.1%) had low TT and normal FT levels and 9 (18.7%) had low TT and FT levels. TT level near the lower limit of normal was detected in 17 (5.3%) patients. Of those, 9 (52.9%) had normal TT and FT levels, 5 (29.4%) had normal TT level and low FT level and 3 (17.6%) had low TT level and normal FT level.

Among patients with biochemical androgen deficiency, 87 (93.5) and 72 (85.7%) had low or normal LH and FSH, respectively. Six (6.5%) had high LH and 12 (14.3%) had high FSH levels in biochemical androgen deficient group. High PRL level was observed in one subject who had also biochemical androgen deficiency.

Tables 1 and 2 exhibit sociodemographic and disease characteristics of participants and laboratory data in biochemical androgen deficient

**Table 2** Laboratory data of patients in studied groups

Variables	Biochemical androgen deficiency		P-value
	Yes (n = 93)	No (n = 226)	
Total testosterone (nmol l <sup>-1</sup> ) <sup>a</sup>	7.3 (6.1–9.0)	14.2 (12.1–18.4)	<0.001
SHBG (nmol l <sup>-1</sup> ) <sup>a</sup>	26.3 (20.5–33.9)	25.0 (18.0–37.7)	0.827
LH (IU l <sup>-1</sup> ) <sup>a</sup>	3.6 (2.1–5.5)	3.9 (2.6–5.9)	0.208
FSH (IU l <sup>-1</sup> ) <sup>a</sup>	3.8 (2.5–6.7)	4.3 (2.7–6.9)	0.569
Prolactin (pmol l <sup>-1</sup> ) <sup>a</sup>	358.9 (251.7–437.7)	361.1 (252.5–498.9)	0.587
Triglyceride (mg dl <sup>-1</sup> ) <sup>a</sup>	152.0 (103.0–216.0)	126.0 (95.0–191.0)	0.022
Total cholesterol (mg dl <sup>-1</sup> ) <sup>b</sup>	186.6 (37.1)	175.9 (38.2)	0.027

Abbreviations: FSH, follicle stimulating hormone; IQR, interquartile range; LH, luteinizing hormone; SHBG, sex hormone binding globulin.

<sup>a</sup>Data were presented as median (IQR).

<sup>b</sup>Data were presented as mean (s.d.).

and normal patients, respectively. There were 37 (11.6%) subjects who took opioids in our study. Opioid use was significantly higher in patients with biochemical androgen deficiency than normal group ( $P < 0.05$ ).

Total cholesterol and TG levels were significantly higher in biochemical androgen deficient men ( $P < 0.05$ ). None of the patients reported alcohol consumption in their history.

In patients with biochemical androgen deficiency, 9(9.8%) had diabetes, and 18 (19.6%) had hypertension. These proportions were not significantly different compared with normal group ( $P > 0.05$ ).

Biochemical tests were not significantly different in patients with cervical, thoracic and lumbosacral levels of SCI and between those with complete and incomplete injury ( $P > 0.05$ ). Age and duration of injury were comparable in three different levels of SCI and complete versus incomplete groups.

Significant correlations between TT level and SHBG ( $r = 0.3$ ,  $P < 0.001$ ), LH ( $r = 0.2$ ,  $P = 0.02$ ), TC ( $r = -0.1$ ,  $P = 0.04$ ) and TG ( $r = -0.3$ ,  $P < 0.001$ ) were found.

Association of independent variables with risk of biochemical androgen deficiency in univariate and multivariate logistic regression analysis are summarized in Table 3. Men who reported opioid use in their medical history had significantly higher odds of having biochemical androgen deficiency in comparison to the rest of the sample (OR = 2.02, 95% CI: 1.01–4.09,  $P = 0.042$ ); however, opioid use was not significant in multivariate model.

## DISCUSSION

SCI in adult men may result in various hormonal changes including testosterone deficiency.<sup>10</sup> Normal physiological concentrations of testosterone may affect the overall health of men. Decrease in serum testosterone levels is associated with several complications. These problems seem to have a negative impact on men's self-confidence, quality of life and well-being.<sup>5</sup>

In current study the overall prevalence of biochemical androgen deficiency was 29.1% among all participants with the mean age of 47 years, which is higher than the prevalence of this problem in healthy men and in patients with ED. The Boston Area Community Health (BACH) survey demonstrated low total ( $< 300$  ng dl<sup>-1</sup>) and free ( $< 5$  ng dl<sup>-1</sup>) testosterone plus one specific symptom (for example, ED) or two nonspecific symptoms in 5.6% of their studied population with the mean age of 47.3 years.<sup>18</sup>

In another study, the prevalence of androgen deficiency in Taiwanese men (mean age = 57.4 years) was 24.1% when TT level  $< 300$  ng dl<sup>-1</sup> was considered as the criterion, and 16.6% considering both TT  $< 300$  ng dl<sup>-1</sup> and FT  $< 5$  ng dl<sup>-1</sup> as the criteria.<sup>19</sup>

Testosterone deficiency in non-SCI men with ED was reported 26.6 and 16.9% in the studies conducted by Somani *et al.*<sup>20</sup> and Corona *et al.*,<sup>21</sup> respectively.

In the two most recent studies, the reported prevalence of low testosterone in men with chronic SCI was close to the findings in present study. In a large series (243 men), Bauman *et al.*<sup>6</sup> reported low TT levels in 46% of their subjects considering a cutoff of 11.3 nmol l<sup>-1</sup>; however, when the cutoff of 10 nmol l<sup>-1</sup> was considered, the prevalence of low TT dropped to 27%. The mean age of participants was similar to that in the present study (48 years). In the report by Barbonetti *et al.*,<sup>22</sup> the prevalence of biochemical androgen deficiency (TT  $< 300$  ng dl<sup>-1</sup>) was 35.3% among their participants with the mean age of 46.7 years. In this study, the prevalence of severe biochemical androgen deficiency (TT  $< 230$  ng dl<sup>-1</sup> with FT  $< 63.4$  pg ml<sup>-1</sup> (220 pmol l<sup>-1</sup>)) was 25.5%. The remaining patients (TT between 230 and 300 ng dl<sup>-1</sup>) had normal levels of FT.

Sex hormone binding globulin abnormality could affect the diagnosis of androgen deficiency based on TT level. In this condition, measurement of FT level is recommended.<sup>7</sup> Accordingly, the high prevalence (43.3%) of testosterone deficiency in men with chronic SCI reported by Durga *et al.*<sup>10</sup> was probably related to the lack of data on SHBG and FT levels. In our studied population, SHBG abnormality was 15%.

So far several studies have investigated serum testosterone and gonadotropins status in men with SCI; however, there have been some inconsistencies with regard to some differences in study methods. One major difference is heterogeneity of time since injury in studies. Clark *et al.*<sup>11</sup> found high prevalence of low serum TT levels (60%) in men with SCI, while 66% of their subjects were in acute phase. Decline in testosterone levels in acute phase of SCI could be related to the acute physical shock,<sup>9</sup> as Celik *et al.*<sup>23</sup> demonstrated that a negative androgen status is not notable after the first year of SCI. In our study, all participants were in chronic phase of SCI and there was no association between time since injury and hormonal values. Durga *et al.*<sup>10</sup> and safarinejad<sup>24</sup> were also not able to find any significant association between these variables in men with chronic SCI.

The neurological level and completeness of injury were not significantly different in biochemical androgen deficient and normal groups. In addition, these injury variables did not affect other hormonal profiles. The association of injury variables and alterations in testosterone and gonadotropins secretion were inconsistent in previous studies.<sup>6,10,11,24</sup> Using different methods for determining neurological level and extent of injury may result in these

**Table 3 Association of independent variables with the risk of biochemical androgen deficiency in logistic regression analysis**

Variables	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (year)	1.01 (0.97–1.04)	0.723	0.98 (0.94–1.02)	0.495
Duration (year)	1.04 (0.99–1.09)	0.095	1.04 (0.98–1.11)	0.115
Severity (incomplete/complete)	1.35 (0.82–2.21)	0.236	1.19 (0.69–2.05)	0.510
SCI.L				
Cervical	Reference	0.208	Reference	0.567
Thoracic	0.93 (0.45–1.94)	0.847	0.95 (0.43–2.07)	0.898
Lumbosacral	1.56 (0.68–3.56)	0.290	1.34 (0.55–3.26)	0.505
Smoking (yes/no)	1.54 (0.91–2.61)	0.106	1.33 (0.74–2.39)	0.324
Opioid use (yes/no)	2.02 (1.01–4.09)	0.048	1.57 (0.72–3.41)	0.251

Abbreviations: CI, confidence interval; OR, odds ratio; SCI.L, spinal cord injury level.

<sup>a</sup>Model 1 = univariate model.

<sup>b</sup>Model 2 = multivariate model (with adjustment). Copyright: 123.

inconsistencies. Our results are in line with those of Barbonetti *et al.*,<sup>22</sup> using the same protocol to define both level and completeness of the lesion.

Dyslipidemia is prevalent in patients with SCI.<sup>25</sup> Testosterone has a key role in lipid metabolism. Indeed, testosterone deficiency is related to elevated TG and TC. In current study, biochemical androgen deficient patients had higher TG and TC levels. This suggests that, testosterone replacement therapy may be beneficial in improving the lipid profile in SCI patients with low serum testosterone level.<sup>26</sup>

Taking opioids has not been considered in most comparable studies,<sup>6,11,24</sup> although it could affect testosterone levels through suppressing the hypothalamic- pituitary- gonadal axis and the secretion of gonadotropin-releasing hormone.<sup>27,28</sup> Chronic pain is one of the common problems in many patients with SCI,<sup>29</sup> and a considerable number of these patients take opioids for pain relief.<sup>10</sup> Some studies have indicated that using long-acting opioids result in androgen deficiency,<sup>7</sup> while others have demonstrated that suppression in testosterone production happens in men taking opioids regularly, regardless of opioid type.<sup>30</sup> In spite of prescribing short-acting opioid analgesics on an as needed basis in our studied population, opioid usage was associated with biochemical androgen deficiency in our SCI patients. Although opioid use was statistically significant in univariate regression, it was not significant in multivariate regression. This indicates that the effect of opioid is probably dependent on other variables in our participants. These data could be useful and worthy of further exploration.

Finally it would be appropriate to mention our study limitations. First, having a retrospective design, our study had some missing data such as body mass index. The second limitation is the lack of a non-SCI matched control group. Despite these limitations, this study had a larger sample size in comparison with other literatures evaluating androgen deficiency in spinal cord injured men. In addition, in relation to low serum testosterone level, we included as many possible factors as our study design permitted.

In conclusion, a substantial proportion of our patients with chronic SCI and ED had biochemical androgen deficiency. This proportion is comparable to recent studies' outcomes on SCI patients. Moreover, opioid use, TG and TC levels were associated with biochemical androgen deficiency in our studied population. Standard screening of androgen deficiency and testosterone replacement therapy are recommended in men with chronic SCI suffering from ED.

#### DATA ARCHIVING

There were no data to deposit.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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