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Prevalence and Etiology of Hypogonadism in Young Men with Chronic Spinal Cord Injury: A Cross-Sectional Analysis from Two University-Based Rehabilitation Centers

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Abstract

Background—Spinal cord injury (SCI) triggers an ‘accelerated aging’ process that may include development of hypogonadism, even among younger men with SCI; however, few studies have investigated the prevalence or etiology of hypogonadism in men with SCI. Young men with SCI are also at increased risk for developing metabolic dysfunction after injury, which may be exacerbated by concomitant testosterone (T) deficiency, thus identifying the prevalence and risk factors for T deficiency in men with SCI is important for their long-term health.

Objective—To investigate the prevalence, risk factors, and etiology of T deficiency (hypogonadism) in otherwise healthy men with chronic, motor complete SCI.

Design—Secondary cross-sectional analysis.

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Setting—Rehabilitation research centers in Washington, DC, and Miami, Florida, USA.

Participants—Men (n=58) aged 18-45 with chronic (≥1 year), motor complete SCI without co-morbidities or use of testosterone therapy.

Methods—Plasma concentrations of hormones were measured using standardized assays. Body composition was assessed with DXA scan.

Main Outcome Measurements—Serum total testosterone and calculated free T.

Results—T deficiency was more common in men after SCI than in a matched cohort of similarly-aged men without SCI (25%, SCI vs 6.7%, non-SCI, P<.001). The risk of hypogonadism appeared to be increased in men with more extensive injury and with higher percent body fat. The majority of men with SCI with low T had low serum LH levels, suggesting that central suppression of the hypothalamic-pituitary-gonadal axis may be the most common etiology of hypogonadism after SCI.

Conclusions—Hypogonadism is more common in young men with SCI than in similarly-aged men without SCI, suggesting that SCI should be identified as a risk factor for T deficiency and that routine screening for hypogonadism should be performed in the SCI population.

Introduction

Data from the National Spinal Cord Injury Statistical Center estimate that up to 300,000 individuals with spinal cord injury (SCI) currently reside in the U.S., with approximately 12,000 new injuries occurring each year [1]. Injuries are most common in individuals between the ages of 15 and 24, with men being four times more likely than women to suffer from SCI [2]. Data from the Christopher and Dana Reeve Foundation (CDRF) [3] corroborate that the SCI is most common in men younger than 50 years.

Individuals living with SCI have a propensity for multiple chronic health conditions and undergo a process of ‘accelerated aging’ after injury [4]. Accelerated aging in men with SCI may include development of hypogonadism, even in young men with SCI; however, few studies have investigated the prevalence or etiology of hypogonadism in this growing population. Indeed, hypogonadism is important to consider in men with SCI because testosterone deficiency may further accelerate the aging process, and may ultimately contribute to increased cardiometabolic risk by promoting the development of sarcopenic obesity, hyperinsulinemia, dyslipidemia, and a heightened inflammatory state, as has been demonstrated in non-injured hypogonadal individuals [5, 6]. Further, androgen deficiency in men with SCI may contribute to sexual dysfunction and infertility, which are common following injury [18].

Prior investigations of serum testosterone concentrations in men after SCI, in both the acute to subacute (<12 months post-injury) and chronic (≥12 months) settings, have suggested that testosterone deficiency is a common complication of SCI in men. However, rates of hypogonadism previously reported in this population range from 10-72% among various studies [7-13]. Differences across studies are likely due to heterogeneous SCI populations, which have varied in participant age, time since injury, and severity of injury. Further, most prior studies failed to evaluate both total and free testosterone levels and thus may have

underestimated hypogonadism when alterations in sex hormone binding globulin (SHBG) levels occurred following SCI. Bauman et al. recently demonstrated a higher prevalence of both low total testosterone (TT) and low free testosterone (fT) in men with chronic SCI compared to the general non-disabled population for each decade of adult life, and greater age-related declines in circulating TT and fT, with striking declines in testosterone (T) levels in men with SCI after the 3rd decade of life [13], providing strong evidence that men with SCI are at heightened risk of developing hypogonadism after injury.

The majority of previous studies investigating gonadal status after SCI have not investigated the etiology of hypogonadism. Studies that have reported serum concentrations of the pituitary hormones LH, FSH, and/or prolactin to determine if hypogonadism is due to a primary testicular defect or is the result of central suppression at the level of the hypothalamus or pituitary are limited by small study populations and report conflicting results, perhaps due to distinct etiologies for hypogonadism that depend on the level of injury or the length of time since injury [8, 11]. For example, Clark et al. [8] found that among 102 men ages 18-82 years (mean±sd, 46±17 years) with acute and chronic SCI, 69% with acute and 40% with chronic SCI had low testosterone, and that low T was significantly associated with elevated prolactin levels; however, they did not measure free T levels or serum gonadotropins. In an earlier study by the same investigators, a high prevalence of low T was seen among men ages 18-92 years (mean±sd, 39±18 years) with acute SCI (<4 months, n=76), but not among men with sub-acute (4-12 months, n=7) or chronic (>12 months, n=9) SCI (% hypogonadal: 83% vs 7% vs. 10%, respectively); however, the investigators again did not assess free T or gonadotropin levels in these patients. Furthermore, in that study, low T was strongly associated with older age, a known risk factor for testosterone deficiency [9]. On the other hand, Celik et al. found decreased free T but no differences in total T levels in men ages 16-71 years (mean±sd, 36±16 years) with acute SCI (n=27), and no differences in free or total T in men with chronic SCI (n=17) compared to age- and BMI control men. Interestingly, with or without differences in T level, men with SCI had significantly higher LH levels compared to controls [10]. Durga et al. demonstrated that 43% of men with chronic SCI had low total T; however, men were older than in other studies (mean age 54 years, range 22-84), free T levels were not assessed, and 30% of men regularly took narcotics, which are known to suppress testosterone production [12]. In a study by Safarinejad, only 10% (8/76) of men ages 31-47 years (mean age 39 years) with chronic SCI (≥10 years) had low total T, although, when compared to a similarly aged control population, the men with SCI had significantly lower mean levels of total T, LH, and FSH. Free T levels were also not assessed in this study [11].

As young victims of SCI are living longer, it is of great interest to their long-term health outcomes to identify and ameliorate factors—such as hypogonadism—that may contribute to their decreased quality of life, and ultimately, increased mortality. Current Endocrine Society Guidelines recommend treating men with signs or symptoms of hypogonadism and biochemical confirmation of hypogonadism (total testosterone <300 ng/dL and/or free T < 9 ng/dL) with testosterone replacement therapy (TRT) unless contraindications exist [14]; however, in men with SCI, gonadal status is frequently not assessed and thus TRT is rarely considered [19, 20]. Furthermore, SCI is not included among medical conditions listed by the Endocrine Society as having a high prevalence of hypogonadism and for which

screening for hypogonadism is recommended [14], despite studies suggesting that the prevalence of gonadal dysfunction in this population may be substantial.

In the current study, we investigated the prevalence of hypogonadism in a cohort of otherwise healthy young men with chronic (≥ 1 year) SCI. We used an age-matched, historical control population of men from the NHANES III trial to compare prevalence of hypogonadism between men with and without SCI [15]. Thereafter, we explored risk factors and etiologies for hypogonadism among our SCI cohort to elucidate potential mechanisms, including age, duration of injury, body adiposity, and function of other hormonal axes, including the adrenal and thyroid axes.

Materials & Methods

Study Subjects

Men between ages 18 and 45 were recruited from an ongoing cross-sectional study evaluating cardiometabolic risk in overall healthy men with motor complete SCI (between C5 and T12) for this secondary analysis. Participants were recruited from the MedStar National Rehabilitation Hospital, Washington, DC, and from the University of Miami Miller School of Medicine, Miami, FL, between 2008 and 2013. We excluded men with self-reported histories of traumatic brain injury, cardiovascular disease, or gonadal dysfunction prior to SCI; men taking medications to treat diabetes mellitus, hyperlipidemia, hypogonadism, or cardiovascular disease (with the exception of antihypertensive medications), men taking any medication that alters serum testosterone levels (such as testosterone replacement therapy, GnRH analogs or 5-alpha reductase inhibitors), and men taking glucocorticoids; men who reported consuming >2 alcoholic drinks per day; men reporting *daily* use of opioid analgesics (*prn* use was considered acceptable); and men with self-reported type 2 or type 1 diabetes mellitus, liver disease, renal disease, heart failure (NYHA Class III or IV), obstructive sleep apnea, prostate cancer, testicular cancer, breast cancer, or benign prostatic hypertrophy (BPH). Men with polycythemia were excluded based on serum hemoglobin and hematocrit concentrations checked at study entry.

Institutional Review Boards at both MNRH and University of Miami approved this study. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Laboratory testing

Laboratory testing was done between 8 and 9 AM after a 10-hour overnight fast. Participants abstained from alcohol and caffeine for 24 hr prior to testing. Total testosterone (TT) was measured by electrochemiluminescense immunoassay (ECLIA)[normal adult male reference range (RR): 300-1100 ng/dL, assay sensitivity 2.5 ng/mL, intra- and inter-assay coefficients of variation (CV): 2.4 and 2.9%, respectively]. ECLIA was used to measure TT because this was the same assay that was used to measure serum TT levels in NHANES III, to which we directly compare data [15]. Free testosterone (fT) was calculated using TT and SHBG concentration by the method of Vermeulen [16], which is a proven, reliable index of bio-available testosterone. Serum concentrations of SHBG (RR: 16-54 nmol/L, sensitivity 0.80

nmol/L, intra-/inter-assay CV: 1.3%, 2.4%), estradiol (RR: 8-42 pg/mL, sensitivity 25 pg/mL, intra-/inter-assay CV: 3.9%, 5.1%), dehydroepiandrosterone-sulfate (DHEAS)(RR 50-550 μg/dL, sensitivity 0.1 μg/dL, intra-/inter-assay CV: 2.3%, 2.4%), LH (RR 1.7-8.6 IU/L, sensitivity 0.1 IU/L, intra-/inter-assay CV: 0.8%, 2%), FSH (RR 1.5-12.4 IU/L, sensitivity 0.1 IU/L, intra-/inter-assay CV: 2.1%, 3.9%), thyroid stimulating hormone (TSH) (RR 0.4-4.2 μIU/mL, sensitivity 0.005 μIU/mL, intra-/inter-assay CV: 3.2%, 4.3%), and cortisol (RR for AM sample, 6.2-19.6 μg/dL, sensitivity 0.036 μg/dL, intra-/inter-assay CV: 1.2%, 2%) were also measured by ECLIA. All reagents were obtained from Roche Diagnostics (Indianapolis, IN) and samples analyzed on a Roche Cobas 6000 analyzer following manufacturer's instructions for calibration and sample processing.

Morning serum concentrations of TT <300 ng/dL and calculated fT <9 ng/dL were considered to be in the hypogonadal range. We categorized study subjects by level of morning TT (<300, 300-500, or >500 ng/dL) and by level of morning fT (<9 or ≥9 ng/dL). Hormone measurements were tested only once for each participant due to the cross-sectional design of this study.

In the NHANES study, serum concentrations of TT were similarly measured in the early morning after an overnight fast using ECLIA, and free testosterone was similarly calculated based on TT, SHBG, and albumin levels using the Vermeulen method [15]. The cutoff used to define low testosterone in the NHANES study was <10.4 nmol/L, which converts to <300 ng/dL, thus we used identical cutoffs to define low TT. The NHANES cutoff for low free T was <0.17 nmol/L, which converts to <5 ng/dL, a very conservative level for defining low fT and significantly lower than the Endocrine Society recommended cutoff of <9 ng/dL [14]. Because we used a cutoff for low fT of <9 ng/dL, we did not compare the prevalence of low fT between our population and the NHANES cohort because this would not be a direct comparison and thus would not answer the question of whether T deficiency is more or less common in men with SCI compared to the general population.

Imaging

Whole body and regional fat and lean body mass were determined by DXA with individuals in the supine position, as described in adults with paraplegia [17], using a Hologic QDR series DXA scanner. Body mass index (BMI) was calculated using mass and height (kg/m^2).

Statistical analyses

Data from study participants were compared by injury category, such that comparisons were made between men with injuries resulting in paraplegia and men with injuries resulting in tetraplegia, in order to determine if severity of injury accounted for differences in demographic characteristics or gonadal status. To compare data by gonadal status, participants were stratified by serum concentrations of total T (<300, 300-500, or >500 ng/dL) and by calculated fT (<9 or ≥9 ng/dL). Normality assumption was satisfied for total T; however, fT, LH and FSH were not normally distributed. Accordingly, the non-parametric Wilcoxon rank sum test and Kruskal–Wallis test were used for comparisons between two fT and three total T groups, respectively.

We derived the prevalence of low TT among men ages 20-49 years in the NHANES cohort by applying the following steps to data in Table 3 of the NHANES study by Rohrmann *et al.* [15]: i) we calculated the approximate number of men in each decade age group (20-29, 30-39, 40-49 years) with low TT by multiplying the prevalence of low TT in each group (%) by the total 'n' for that group (i.e., in the age group 30-39, 4.8% prevalence of low TT among 938,276 men: [.048 × 938,276]=45,037 men between ages 30-39 with low TT), ii) we calculated the prevalence of low TT for the entire group of men ages 20-49 years by adding the number of men with low TT in each decade age group, dividing by the total 'n' for men ages 20-49 years, and multiplying by 100 to acquire a percentage (i.e., [10,357+4,5037+165,457 ÷ 450,313+938,276+1,901,808] × 100 = 6.7%).

Means and standard deviations for continuous variables and frequencies and percentages for categorical variables were calculated for all groups. For continuous variables, the differences in means between groups were tested by ANOVA when normality assumption was satisfied and by the non-parametric Kruskal–Wallis test when normality assumption was not satisfied. Chi-square and Fisher exact tests were used to investigate the differences between categorical variables. Fisher's exact test was used to compare the prevalence of hypogonadism (TT<300 ng/dL) between men with SCI in our cohort and historical data from healthy, non-SCI men aged 20-49 years in NHANES III. P<.05 was considered statistically significant.

Results

Participant demographics

By injury level—A total of fifty-eight (58) men between ages 18 and 45 who had enrolled into the parent study met our inclusion/exclusion criteria and agreed to participate in this secondary cross-sectional analysis. Of the 58 study participants, mean (range) age was 33.8 (23-45) years and mean duration of injury was 4.6 (1.2-40) yrs. Forty subjects (69%) were classified as paraplegic and 18 (31%) as tetraplegic. There were no differences in participant age, duration of injury, race, TT or fT levels, or percentage with low or normal TT or fT between men with paraplegia and men with tetraplegia. Of note, men with tetraplegia had an approximately 2-fold higher prevalence of TT<300 compared to men with paraplegia, although this difference did not reach statistical significance (Table 1). There was also a non-significant trend toward decreased SHBG concentrations in men with tetraplegia versus paraplegia (P=.08) (Table 1). In accordance with lower SHBG concentrations, men with tetraplegia had significantly higher body fat percentage (37±9%) compared to men with paraplegia (30±11%, P=.02), despite similar body mass index (BMI) (26±5, tetraplegia *vs* 25±3 kg/m^2, paraplegia, P=.60).

By gonadal status—We also compared demographic characteristics among study participants after stratifying by serum concentrations of total T (<300, 300-500, or >500 ng/dL, Table 2a) and fT (<9 or ≥9 ng/dL, Table 2b). There were no differences in participant age, race, duration of injury, or level of injury (paraplegia *vs* tetraplegia) among men within the 3 total T tertiles. Men with TT<300 ng/dL exhibited significantly lower SHBG concentrations than did men in the other two TT groups (mean±sd SHBG (nmol/L): 20±7

TT<300 vs 26±11, TT 300-500 vs 36±14, TT>500, P<.01)(Figure 1). In accordance with the differences in SHBG levels, there were significant differences in percentage body fat (as measured by DXA), but not in BMI, among the 3 total T tertiles. Specifically, body fat percentage was highest in men with TT<300, lowest in men with TT>500, and intermediate in men with TT between 300 and 500 ng/dL, despite similar BMI's among the 3 TT groups (Figure 1). When comparing men with low compared to normal fT, we likewise found no differences in race, duration of injury, or level of injury between men within the two fT groups, however, men with low fT were significantly older than men with normal fT (Table 2b). Similar to our data comparing the three total T groups, men with fT<9 ng/dL had higher percentage body fat compared to men with fT≥9 ng/dL (mean±sd %body fat: fT<9, 37±12% vs fT>9, 30±9%, P=.02)); however, men with low fT also had higher BMI compared to men with normal fT (mean±sd BMI, 29±5 vs 23±3 mg/kg2, P=0.01) and there were no differences in SHBG levels between the two fT groups (mean±sd SHBG (nmol/L): 27±14, fT<9 vs 32±17, fT>9, P=.12).

Prevalence of hypogonadism among men with chronic SCI versus control subjects without SCI

Hypogonadism was present in 15 of 58 (25%) of men with SCI in our cohort based on TT<300 ng/dL and 21 of 58 (36%) of men based on fT <9 ng/dL. Twenty-two percent (13 of 58) of men had both low TT *and* low fT, and 40% (23 of 58) had either low TT *or* low fT (Table 3). The prevalence of low total T among men with chronic SCI was significantly higher compared with that in similarly aged men from NHANES III (25%, SCI vs 6.7%, NHANES, P<.001)[15].

Etiology of hypogonadism in men with chronic SCI

We measured serum concentrations of the pituitary hormones luteinizing hormone (LH), which promotes steroidogenesis, and follicle stimulating hormone (FSH), which promotes gametogenesis, in men with SCI to determine the putative etiologies of hypogonadism among participants. Overall, mean serum LH concentrations were significantly lower in men with low total T and low fT compared to men with normal total T and normal fT, respectively. Among men with low total T or low fT, FSH concentrations were not different compared to men with normal TT or fT levels, which is consistent with the function of FSH as a gametogenic rather than a steroidogenic hormone (Table 4a). In this cohort, 9 of 23 (39%) men exhibited low TT or low fT and low LH and FSH, indicating secondary (central) hypogonadism; 5 of 23 (22%) had low TT or low fT with high LH and/or FSH levels, consistent with primary hypogonadism; and 9 of 23 (39%) exhibited low TT or low fT with normal FSH and LH, consistent with a mixed etiology for their hypogonadism. Twelve (12) of 35 (34%) men with normal TT and normal fT exhibited elevated LH or FSH, suggesting compensated hypogonadism.

Relationships between total or free T level and estradiol, TSH, cortisol, and DHEAS levels in men with chronic SCI

When comparing men in our study based on total T <300, 300-500, or ≥500 ng/dL, we found no differences in serum concentrations of estradiol, TSH, cortisol, or DHEAS. Likewise, there were no differences in serum TSH, cortisol, or DHEAS levels between men

with low versus normal fT. Serum estradiol concentrations were significantly lower in men with low fT versus normal fT (Table 4a).

Relationships between injury level and LH, FSH, estradiol, TSH, cortisol, and DHEAS concentrations in men with chronic SCI

Serum LH concentrations were significantly lower in SCI men with tetraplegia versus paraplegia (Table 4b), whereas there were no significant differences in FSH, estradiol, TSH, cortisol, or DHEAS levels between the two groups. Although neither TT nor fT values differed significantly between men with paraplegia and tetraplegia, mean TT and fT values were lower (Table 4b), and there was a nonsignificant trend toward a higher prevalence of both low total T and low fT among men with tetraplegia (Table 1). The lower testosterone levels we observed among men with tetraplegia are consistent with a trend toward lower SHBG levels and significantly higher body fat percentage among men with tetraplegia compared to men with paraplegia that we demonstrated (data above).

Discussion

In this cross-sectional analysis of a well-characterized cohort of otherwise healthy young men with SCI, we found that chronic SCI is associated with a 3.7-fold higher prevalence (25%) of low TT compared to that in an aged-matched population from NHANES III without SCI. We detected an even higher prevalence of hypogonadism among young men with SCI when low fT levels were considered (36%). These data suggest that SCI, particularly with tetraplegia, is a significant risk factor for the development of male hypogonadism, even at young adult ages, and further suggest that individuals with chronic SCI warrant screening for testosterone deficiency post-injury. Importantly, our findings support and extend prior studies showing a high prevalence of testosterone deficiency in men with SCI [7-13].

There are limitations to comparing the prevalence of low total T between our cohort of men with SCI and the NHANES cohort. First, our exclusion criteria were more restrictive compared to the NHANES study. Specifically, we included only men with SCI who would be appropriate candidates to receive testosterone replacement therapy (TRT) should they be found to have testosterone deficiency, i.e., we excluded men with contraindications to TRT such as known prostate disease, male breast cancer, severe heart failure, or polycythemia, among others. We also excluded men with chronic disease such as diabetes mellitus, obstructive sleep apnea, and hyperlipidemia, which are highly associated with obesity. Thus, our exclusion criteria may have skewed our population to be overall healthier compared to the NHANES population, with less comorbid disease and less obesity; however, we were not able to assess rates of chronic disease or obesity among the NHANES participants for whom testosterone levels were assessed. That said, one would expect that a group of men who are overall more fit (with the exception of SCI) would be *less likely* to have T deficiency, given that i) chronic disease states suppress the hypothalamic-pituitary-testicular (HPT) axis and ii) obesity lowers SHBG levels and thus is associated with decreased total T levels. Second, there were racial/ethnic differences between our cohort and NHANES. Specifically, compared to our cohort with SCI, NHANES had a significantly higher proportion of

Caucasian participants age 20-49 (~76% NHANES *vs* 21% SCI) and a lower proportion of black and Hispanic participants (~10% NHANES *vs* 38% SCI and ~6% NHANES *vs* 41% SCI, respectively). A prior analysis of NHANES III data showed that testosterone levels did not differ between black and Caucasian men, and were slightly higher in Hispanic Americans compared to blacks and Caucasians [21]. Another recent study found no differences in serum T levels among black, Hispanic, and Caucasian men age 30-79 randomly sampled from a community-based population [22]. Given these data, we believe that the racial differences between our study and NHANES did not significantly impact the differences we saw in prevalence of T deficiency. In fact, our study potentially *under-estimated* the prevalence of T deficiency in our SCI cohort given that 41% of our study population was Hispanic, which has been associated with higher T levels [21].

Our findings of a high prevalence of hypogonadism among men with chronic SCI are consistent with the data of others who have measured circulating testosterone concentrations in men with SCI [7-13]. Our data support and extend these studies by investigating not only the prevalence of hypogonadsim among a well-characterized, healthy population of young men with chronic SCI (rather than older cohorts with various co-morbidities in prior studies), but also by investigating etiologies and risk factors for T deficiency in this population. We found that older age, higher level of injury (tetraplegia compared to paraplegia), lower SHBG values, and higher percent body fat were risk factors that individually increased the risk for low total T or low fT in men with chronic SCI. Increased adiposity is associated with decreases in SHBG levels [14], thus the lower total T levels in men with higher percent body fat that we observed are likely due, at least in part, to decreased SHBG concentrations. Altered SHBG concentrations would not, however, explain decreases in free T levels among men with increased percent fat. Most prior studies have not assessed free T levels in men with SCI, thus they could not account for potential changes in total T levels due to decreased SHBG.

We also found that percent body fat is a better predictor of low T compared to BMI in the SCI population, which reconfirms previously reported data indicating that BMI is an unreliable determinant for obesity, a risk factor for low T, in SCI individuals [23]. We found increased percent body fat and a trend toward lower SHBG levels in men with tetraplegia compared to men with paraplegia, without statistically significant differences in the prevalence of low TT or low fT between tetraplegic and paraplegic men. That said, the differences in body adiposity and serum SHBG concentrations that we observed between tetraplegic and paraplegic men suggest that the risk of developing hypogonadism and metabolic complications after SCI may increase with more extensive levels of injury.

Considering our relatively small sample size and varying gonadotropin levels among men in our cohort with low TT or low fT, we are unable to determine with certainty the most common etiology of hypogonadism after chronic SCI; however, we can speculate as to potential mechanisms based on our findings. As a group, more men with SCI exhibiting low TT or low fT had decreased LH and FSH levels compared to men with normal TT and fT, suggesting that a common mechanism for testosterone deficiency in the male SCI population may be central suppression of the hypothalamic-pituitary-testicular axis. However, a subset of men in our cohort had low TT or low fT with high LH and FSH levels, suggesting

primary hypogonadism, and a subset with low TT or low fT had normal LH and FSH levels, perhaps due to mixed primary and secondary hypogonadism. Further, among men with SCI with normal TT and normal fT, a subset had elevated FSH and LH levels, suggesting compensated hypogonadism. Together, these data indicate that there may be multiple pathophysiological causes of hypogonadism after spinal cord injury, but a larger study is needed to characterize the precise temporal pattern of changes in HPT axis function that occur after SCI. The etiology of hypogonadism among men with SCI may also be affected by level of injury, as men with tetraplegia exhibited significantly lower LH concentrations than men with paraplegia, suggesting a higher risk of suppression of pituitary gonadotropin secretion with more central levels of injury. We were unable to measure serum prolactin levels in our study participants to determine if hyperprolactinemia may have been associated with central suppression of the HPT axis in men with SCI. Additionally, we cannot discount that other factors, such as interruption of afferent sensory sexual inputs or lack of sexual activity, may have contributed to low T in young men with SCI with evidence of primary hypogonadism [18]; however, given the design of our study, we were unable to assess sexual function.

We found no differences in duration of injury in men with low TT or low fT versus normal TT or fT. Men with low fT were significantly older than men with normal fT (39 ±11 vs. 31 ± 10 yrs, P=.01), and there was a non-significant trend toward older age in men with low TT versus normal TT levels (TT<300 ng/dL, 40±12; TT 300-500, 33±12; TT>500, 32±9 yrs, P=.20). The differences we saw in the effects of age on TT *vs* fT may be due to increases in SHBG levels that occur with age [14]. In support of this reasoning, SHBG levels were higher in men with normal TT compared to men with low TT, and this was primarily due to higher SHBG levels among men with TT levels in the highest TT stratum (>500 ng/dL). SHBG concentrations are also reported to be inversely associated with body adiposity, and aging is a risk factor for development of sarcopenic obesity, a process that is accelerated in men after SCI [4]. Taken together, our data indicate that age, even before age 45, contributes to development of hypogonadism among young men with SCI. These findings support previous data demonstrating accelerated age-related declines in androgen production after SCI [13]. The contribution of aging is likely due, at least in part, to development of sarcopenic obesity (increase in percent body fat and decrease in lean body mass without changes in BMI) and reductions in SHBG concentrations in the post-injury period.

Serum estradiol concentrations were lower in men with decreased versus normal fT, whereas there were no differences in estradiol levels between men with low versus normal TT. Bioavailable testosterone is converted to estradiol by aromatase enzymes, thus the reduction in estradiol levels among men with low fT but not low TT suggests that fT may be a more valid measure of gonadal function in the SCI population. Taken together with post-injury differences in serum SHBG concentrations and body adiposity, an approach that measures both total TT and fT appears warranted when evaluating for androgen deficiency in men with SCI.

Serum concentrations of TSH, cortisol, and the adrenal androgen DHEAS did not differ between men with low versus normal TT or fT, suggesting that hypogonadism in men with SCI is not associated with abnormalities in those hormone axes. We also found no

differences in values of TSH, cortisol, or DHEAS in men with paraplegia versus tetraplegia, although there was a non-significant trend (P=.08) toward lower cortisol levels in men with tetraplegia, similar to the trend toward lower TT, but not lower fT, observed in this same group. One possible explanation for these differences might be decreased levels of SHBG and cortisol binding globulin (CBG) after a cervical injury. We did not measure cortisol binding globulin (CBG) concentrations in our study participants, though our finding of a clear trend toward decreased SHBG levels in men with tetraplegia versus paraplegia suggests that CBG levels may also be decreased in individuals with tetraplegia, resulting in lower serum concentrations of total cortisol.

Prolonged testosterone deficiency in men is associated with a myriad of negative health consequences, including insulin resistance, dyslipidemia, cardiovascular disease, sarcopenic obesity, depression, and decreased overall quality of life [5, 6]. Our data showing an increased prevalence of hypogonadism among young men with chronic SCI support the need for a guideline recommending that men with SCI undergo routine screening for testosterone deficiency. Current Endocrine Society Guidelines recommend screening of high-risk populations for hypogonadism, including men with HIV-associated weight loss, chronic medical illnesses such as chronic kidney disease and COPD, men with histories of non-traumatic fractures occurring at young ages, and men taking long-term glucocorticoid therapy [14]. Currently, however, spinal cord injured men are not identified as one of these “high risk” populations. Based on our data and the data of others, men with SCI have a propensity for developing androgen deficiency compared to the general population, thus warranting inclusion of the SCI population among other high-risk populations that should be screened for hypogonadism. We were not able to assess our study participants for specific signs and symptoms of hypogonadism, as recommended by current guidelines [14], however, given the non-specific nature of many symptoms of hypogonadism, the potential overlap with symptoms that occur due to SCI itself (e.g., fatigue, depressed mood, erectile dysfunction), and/or possible changes in typical signs and symptoms due to the neurologic impairment, we feel that demonstration of significantly higher rates of biochemical hypogonadism among men with SCI warrants screening in this population.

Limitations of our study include the small sample size (n=58); single (rather than multiple) measurements of serum testosterone and gonadotropin levels for each participant; lack of detailed physical exam or history to assess potential physical manifestations of low T, sexual developmental history, or symptoms of low T; and inability to assess sexual function in our study subjects. Strengths of this study include ability to asses multiple hormone parameters in each study subject, including reproductive, thyroid and adrenal axis hormones; measurement of both total and free testosterone levels; a well-characterized, overall healthy, young population of men with chronic SCI; and ability to accurately assess body composition, particularly percent body fat, using DEXA measurements.

Overall, our data suggest a need for more active primary surveillance of the SCI population for gonadal dysfunction at earlier chronological ages than in the general population, or soon after injury. In this regard, Bauman *et al.* also showed a significantly higher prevalence of low TT and low fT in men with chronic SCI, as well as greater age-related declines in circulating T levels, especially in the 3rd decade of life and thereafter [13]. Our data build on

existing support for screening men with SCI for testosterone deficiency beginning at least 1 year post-injury and/or by the 3rd decade of life. It remains to be determined how soon after spinal injury changes in gonadal function begin to appear, or whether interventions that can help curtail the declines in cardiometabolic health that occur after chronic SCI can improve life expectancy or quality of life for these individuals. Indeed, further investigations are needed to determine the extent to which T deficiency contributes to the known accelerated aging process in this population, including development of metabolic syndrome and increased cardiovascular disease risk, and whether physiological T supplementation may help reduce cardiometabolic risk as well as overall morbidity and mortality among hypogonadal men with chronic SCI.

Conclusion

Hypogonadism is more common in young men with SCI than in similarly-aged men without SCI, suggesting that SCI should be identified as a risk factor for T deficiency and that routine screening for hypogonadism should be performed in the SCI population.

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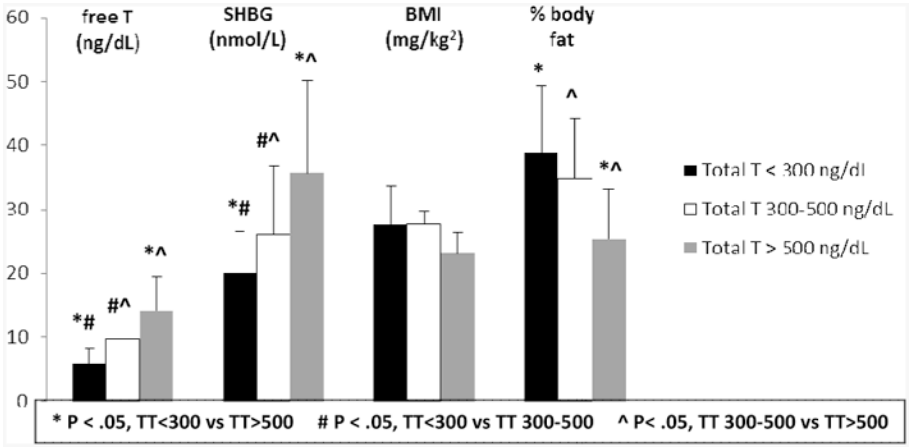

Figure 1.

Free Testosterone, SHBG, BMI, and Percent Body Fat in SCI Men with Total Testosterone (TT) <300, TT 300-500, TT >500 ng/dL.

Table 1

Demographic Characteristics and Serum Testosterone Concentrations in Men with Paraglegia and Tetraplegia.

Characteristics	**Injury level**		
	Paraplegia N=40(%)	**Tetraplegia N=18(%)**	**P value**
Age (years)	35±12	31±8	.34
Duration of Injury (months)	22±12	17±8	.11
Race			.35
Caucasian	7(18)	5(28)	
African Am	14(35)	8(44)	
Hispanic	19(48)	5(28)	
TT (ng/dL)			.27
<300	8(20)	7(39)	
300-500	14(35)	5(28)	
>500	18(45)	6(33)	
fT			.26
<9 ng/dL	13(33)	8 (44)	
>9 ng/dL	27(67)	10(56)	
TT (ng/dL) (mean±sd) [RR 300-1100]	490±241	386±182	.14
SHBG nmol/L (mean±sd) [RR 16-54]	32±18	23±9	.08
fT ng/dL (mean±sd)	11±5	9±4	.44

*P<0.05

TT=Total Testosterone; fT=Free Testosterone; SHBG=Sex Hormone Binding Globulin

Table 2a

Demographic Characteristics and Injury Level in Men with SCI with serum concentrations of TT<300, 300-500, and >500 ng/dL.

Characteristics	**Total Testosterone (ng/dL)**			
	<300 N=15	**300-500 N=19**	**>500 N=24**	**P value**
Age (years)	39±12	33±11	32±9	.24
Duration of Injury (months)	22±14	23±10	20±10	.74
Race				.06
Caucasian	6(40)	1(5)	5(21)	
African Am	6(40)	5(26)	11(46)	
Hispanic	3(20)	13(69)	8(33)	
Injury level				.27
Paraplegia (n=40)	8 (20)	14 (35)	18 (45)	
Tetraplegia (n=18)	7 (39)	5 (28)	6 (33)	

*P<0.05

TT=Total Testosterone

Table 2b

Demographic Characteristics and Injury Level in Men with SCI and serum concentrations of fT<9 and ≥9 ng/dL.

Characteristics	**fT (ng/dL)**		
	<9 N=21	**≥9 N=37**	**P value**
Age (years)	39±11	31±10	<.01 *
Duration of Injury (months)	24±14	20±9	.14
Race			.08
Caucasian	7(36)	4(11)	
African American	6(32)	13(35)	
Hispanic	6(32)	18(49)	
Injury level			.26
Paraplegia (n=40)	13 (33)	27(67)	
Tetraplegia (n=18)	8(44)	10(56)	

* P<0.05

fT=Free Testosterone

Table 3

Prevalence of low Total T (TT) (<300 ng/dL) and low free T (fT) (<9 ng/dL) in 58 men with motor complete chronic SCI, age 18-45.

Total N =58	TT<300 ng/dL	fT <9ng/dL	Low TT OR low fT	Low TT AND low fT
N	15	21	23	13
%	25%	36%	40%	22%

TT=Total Testosterone; fT=Free Testosterone

Table 4a

Serum hormone concentrations in Men with SCI with Total Testosterone (TT) <300, 300-500, or >500 ng/dL, and with Free Testosterone (fT) <9 or ≥9 ng/dL

Total T (ng/dL)	**<300 N=15**	**300-500 N=19**	**≥300 N=24**	***P***
LH (IU/L) [RR 1.7-8.6]	4.6±2.4	7.2±4.3	7.3±3.9	.02 *
FSH (IU/L) [RR 1.5-12.4]	6.4±5.0	7.9±10.6	6.8±4.9	.41
Estradiol (pg/mL) [RR 8-42]	27.7±7.5	27.6±7.0	31.2±11.7	.60
TSH (μIU/mL) [RR 0.4-4.2]	1.9±1.2	2.3±3.0	2.0±1.0	.68
Cortisol (μg/dL) [RR 6.2-19.6]	13.2±5.7	13.5±4.9	16.5±6.0	.12
DHEAS (μg/dL) [RR 50-550]	257±126	292±122	263±100	.69
Free T (ng/dL)	**<9 N=21**		**≥9 N=37**	***P***
LH (IU/L)	5.3±4.0		7.3±3.6	.008 *
FSH (IU/L)	7.6±7.9		6.71±6.8	.74
Estradiol (pg/mL)	25.1±5.4		31.4±10.4	.013 *
TSH (μIU/mL)	2.3±2.9		2.0±1.1	.75
Cortisol (μg/dL)	15.2±5.7		14.3±5.8	.57
DHEAS (μg/dL)	252±120		282±110	.31

* P<0.05

LH=Luteinizing Hormone; FSH=Follicle Stimulating Hormone; TSH=Thyroid Stimulating Hormone; DHEAS= dehydroepiandrosterone-sulfate

Table 4b

Serum hormone concentrations in men with SCI based on level of injury.

	Injury level		
Hormone level (mean±sd)	**Paraplegia N=40**	**Tetraplegia N=18**	**P value**
Total T, ng/dL [RR 300-1100]	490±241	386±182	.14
Free T, ng/dL	11.2±5.3	9.4±3.9	.44
LH, IU/L [RR 1.7-8.6]	7.2±4.2	4.9±1.8	<.05*
FSH, IU/L [RR 1.5-12.4]	8.1±8.1	4.3±3.7	.08
Estradiol, pg/ml [RR 8-42]	30.9±10.1	27.0±9.4	.12
TSH, μIU/ml [RR 0.4-4.2]	2.2±2.3	1.7±0.7	.86
Cortisol, μg/dL [RR 6.2-19.6]	15.4±5.7	12.40±5.0	.07
DHEAS, μg/dL [RR 50-550]	260±117	308±108	.14

*P<0.05

T=Testosterone; LH=Luteinizing Hormone; FSH=Follicle Stimulating Hormone; TSH=Thyroid Stimulating Hormone; DHEAS=dehydroepiandrosterone-sulfate