Published in final edited form as:

Int Urol Nephrol. 2015 January ; 47(1): 47–52. doi:10.1007/s11255-014-0864-1.

Is Testosterone Deficiency A Possible Risk Factor For Priapism Associated With Sickle Cell Disease?

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Abstract

Purpose—The purpose of this study was to determine the association of testosterone deficiency and priapism in adult men with SCD.

Methods—A cross-sectional study of 50 adult men with homozygous S SCD was performed. All patients had early morning blood taken for total and free testosterone, FSH, LH, prolactin, lipid levels, LDH and hematological indices. Patients completed an interviewer-administered questionnaire regarding priapism frequency, duration, and treatment. Testosterone deficiency was defined as a serum total testosterone < 12 nmol/L (346 ng/dl).

Results—The mean age of the study population was 34.2 ± 8.9 years. Priapism was noted in 24 (48%) patients and was most frequently seen in men between ages 18–25 years. Testosterone deficiency was observed in 11 of 50 (22 %) of all patients, and particularly in 6 of 24 (25%) patients with histories of priapism. There was no difference in mean total testosterone levels in patients with and without a history of priapism (16.7 ± 4.9 nmol/L and 15.4 ± 5.9 nmol/L, respectively) ($p=0.43$). Similarly, there was no difference in serum LH and FSH levels based on history of priapism.

Conclusion—Testosterone deficiency is prevalent in patients with SCD; however, we did not identify an association based on a history of priapism. Larger, prospectively gathered data is needed to define the priapism profile of SCD patients with testosterone deficiency.

Keywords

SCD; hypogonadism; erection; ischemic priapism

INTRODUCTION

Priapism is defined as a persistent penile erection that continues beyond, or is unrelated to, sexual stimulation [1]. Sickle cell disease (SCD) is a strong risk factor for priapism and occurs in up to 42% of men with the disorder [2]. Patients with SCD typically experience ischemic priapism, characterized by poor or absent cavernosal blood flow. Priapism is a compartment syndrome of the penis and hence a urological emergency that, if prolonged, can result in erectile dysfunction [3]. Pryor reported that 90% of men with ischemic priapism over 24 hours in duration experience erectile dysfunction [3].

Low serum testosterone has also been described in males with SCD [4,5]; however, the exact aetiology is unknown. The mechanism of action may be via a primary testicular pathology, secondary to testicular infarcts [5]. Alternatively, several studies have also reported possible pituitary infarction as a secondary cause [6]. Despite the cause, the effects of low testosterone on young and adolescent males include delayed growth and development [7], and in men, manifests with reduced libido and erectile dysfunction [8].

Appropriately, there is great interest in understanding the mechanism underlying this condition, particularly in the setting of SCD. The role of testosterone in mediating normal erections is known [9]. Androgens are critical for maintaining normal expression of phosphodiesterase (PDE) type 5 in the penis. Androgen deprivation reduces PDE 5 expression in animal models while testosterone supplementation restores PDE5 gene and protein expression [10]. However, the association of serum testosterone levels and priapism is unknown. There are some who believe that high circulating levels of serum testosterone may trigger priapism episodes [11,12]. Drugs such as oestrogens [13], anti-androgens [14] and ketaconazole [15], which serve to reduce serum testosterone toward castrate levels, have been used in the past to treat or prevent priapism episodes. However, high circulating levels of testosterone in patients with priapism and SCD have never been demonstrated.

The male with SCD and priapism serves as a relevant model to study the molecular aetiological mechanisms involving priapism. However, we question the presumed understanding that androgens are effectors of priapism in this population and conjecture oppositely, that low testosterone levels are commonly associated with priapism. We sought to evaluate the possible association of testosterone deficiency and priapism in adult men with SCD.

METHODS

Patients

This was a cross-sectional study and patients were recruited from July-October 2010. A convenience sample of fifty (50) male patients with homozygous S SCD, attending the Sickle Cell Unit, University of the West Indies, Jamaica for health maintenance visits were recruited. The Sickle Cell Unit of the University of the West Indies, located in Kingston, Jamaica is the only specialized center providing comprehensive care for persons with SCD in the English-speaking Caribbean. The center is a non-referral unit and any patient with any of the sickle cell diseases who wishes to attend is registered and provided with clinical care.

All patients were in a clinically steady state. Exclusion criteria included acute illnesses, endocrine disorders (eg hypothyroidism, hyperthyroidism, diabetes, and metabolic syndrome), and use of testosterone therapy.

Measurement

All patients had blood drawn, between 8:00 and 11:00 am, for determination of total and free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, complete blood count (CBC), lactate dehydrogenase (LDH) and lipid profile (serum triglycerides, High density lipoprotein {HDL} and Low density lipoprotein {LDL} cholesterol). Serum was separated immediately and stored at -20°C until assayed. Serum lipid profile and CBC were obtained due to the commonly associated finding of increased LDL, reduced HDL and anemia with low testosterone levels. Quantitative estimation of LDH was performed as it is a commonly used biomarker of SCD activity [16].

Total testosterone was measured with the IMMULITE 2000 Analyzer chemiluminescent enzyme immunoassay. Reference laboratory normal total testosterone ranged from 12.5–38.1 nMol/L (360–1098 ng/dl). Testosterone deficiency was defined as serum total testosterone < 12 nMol/L (346 ng/dl). Though there is no generally accepted cut-off value of plasma total testosterone for defining androgen deficiency, a previously reported normal total testosterone between 12 and 35 nmol/L was used to define our cut-off level [17]. Wu et al. defined testosterone deficiency as a total testosterone less than 11 nmol/L [18]. Free testosterone was measured with the Coat-A-Count ^{125}I radioimmunoassay. Bioavailable testosterone levels were not measured.

Questionnaire

Patients completed an interviewer-administered, non-validated questionnaire regarding history of priapism, age at first episode, frequency and duration of episodes, and treatment (medical and/or surgical). Priapism was defined as a persistent penile erection that continues beyond, or is unrelated to, sexual stimulation. The definition included patients with major ischemic episodes and stuttering episodes.

Ethical Approval

Ethical approval was granted by the Institutional Review Board at the University of the West Indies, Kingston, Jamaica.

Main Outcome Measures

Outcome measures included frequency of priapism and the association of testosterone deficiency and priapism.

Statistical Analysis

Data were analyzed using Statistical Analysis Software, version 9.2 (SAS Institute, Cary, NC). Means were compared between groups by using the t test and non-parametric alternate if the distribution could not be normalized or the variance was not equal. Categorical data was compared using the Chi-square test where appropriate. All statistical tests were two sided and $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of the study population was 34.2 ± 8.9 years. Twenty-four (48%) patients reported a history of priapism (Table 1), with the majority experiencing first onset between ages 18–25 years and most episodes during sleep. Priapism episodes most commonly lasted for 1 hour after awakening from sleep (Table 1). There was no difference in age or serum haemoglobin, LH, FSH, total or free testosterone levels based on a reported history of priapism (Table 2).

The mean total testosterone for all patients was 16.0 ± 5.4 nMol/L. Testosterone deficiency was observed in 11 of 50 (22 %) of all patients, specifically, 6 of 24 (25%) patients with priapism vs 5 of 26 patients without priapism ($p = 0.623$) (Table 3). There was no difference in mean LDH levels in men with normal testosterone levels (1335.2 ± 513.2) vs those with testosterone deficiency (1246.2 ± 250.2) ($p = 0.89$) (not shown).

Of the patients who reported a history of priapism, there was no difference in total or free testosterone levels relative to frequency, number and duration of priapism episodes. Free testosterone level was appreciably, but not significantly, lower in patients having >30 min of priapism episodes after awakening from sleep (297 pMol/L) than in patients having <30 min of priapism episodes after awakening from sleep (409 pMol/L) ($p = 0.09$).

DISCUSSION

To our knowledge this is the only study exploring the possible association between testosterone deficiency and priapism in the SCD population. Although some believe that androgens positively influence priapism [11,12], high circulating levels of testosterone in patients with priapism and SCD have never been demonstrated. Rather, both priapism and testosterone deficiency are commonly observed in the SCD population. Our study results, demonstrating that 48% of the sampled men report a history of this priapism, are consistent with previous data that this disorder is common in men with SCD in Jamaica, keeping with prior data showing a 42% prevalence in this population [2]. Similarly, we confirmed that testosterone deficiency is common in SCD with 22% of the sampled men having the deficiency [4,5]. Among SCD patients with histories of priapism, as much as 25% had testosterone deficiency. Despite these elevated rates, no significant difference was found regarding testosterone deficiency between groups with and without priapism in this study. Additionally, no significant difference was realized regarding testosterone levels and either LDH levels or aspects of priapism history (episode frequency, number, and duration). Although we were unable to realize an association between these phenomena, an understanding of the role of androgens in erection regulatory mechanisms continues to emerge.

Androgens affect various aspects of penile growth, development and function [9,10], which seem to be mediated through dihydrotestosterone (DHT). The importance of androgens is indicated by the fact that surgical or medical castration results in impaired erectile function, which may be reversed by testosterone therapy [19]. Androgens regulate specific bio-molecular events involved in erections as well as normal corporal vascular homeostasis. The

nitric oxide (NO) synthase/cyclic guanosine monophosphate (NOS/cGMP) system is critical for normal erectile function. NO mediates corporal smooth muscle relaxation [20]. Androgens regulate the expression of various isoforms of NOS in the corpora cavernosa [9,10]. Testosterone deficiency results in a reduction of NOS activity [9]. Phosphodiesterase type 5 (PDE5) terminates NO-induced cGMP-mediated smooth muscle relaxation [21]. Castration reduces the expression and activity of PDE5 in animal models and androgen therapy reverses these functions [22].

Androgens also maintain penile corporal trabecular smooth muscle structure as well as the corporal extracellular matrix (ECM). The effects on the ECM alter the fibroelastic properties of the corpora and, subsequently, penile tissue compliance and vascular flow [9]. Structure and function of pelvic ganglion nerves are maintained through the actions of androgens [23]. In testosterone deficient states, penile corporal structure, molecular signaling and pelvic nerve functions are altered which can subsequently lead to erectile dysfunction.

The molecular mechanisms underlying priapism related to low testosterone in men with SCD has not been described. However, we theorize that they involve molecular dysfunction of the NOS/cGMP system. This science has been previously described in the sickle cell animal model [24]. SCD is a haemoglobinopathy that results in generalized vascular dysfunction and induces abnormal NOS activity/NO bioavailability in the penis [24]. Dysregulated NO function affects the regulatory basis for cavernosal smooth muscle tone which interferes with corporal detumescence. Transgenic sickle-cell mice have reductions in penile NOS/cGMP signaling leading to deficient PDE5 and uncontrolled erectile responses [24]. The RhoA/Rho-kinase vasoconstrictive pathway that opposes NO signal transduction pathway is also downregulated when NO signaling is reduced [25]. When the cavernosal smooth muscle relaxant system is uncontrolled, the response to normal erectile stimuli (sexual related or nocturnal) is a prolonged penile erection. Hypoxia, acidosis and glucopenia seen in SCD and other hematological dyscrasias also alter cavernosal smooth muscle tone [26]. We hypothesize that since testosterone is required for the regulation of the NOS/cGMP pathway, which becomes further dysregulated in low testosterone states, these previously described effects are further deranged in men with SCD and low testosterone levels. Hence, low testosterone levels may actually increase the risk for priapism in men with SCD; however, we recognize that alternative molecular mechanisms may contribute to the presentation of priapism [26–28].

LIMITATIONS

We acknowledge several possible limitations of this investigation. Although our study did not suggest a risk association of priapism and low testosterone levels, we realize that a larger prospective trial would offer a more robust basis from which to adequately evaluate this hypothesis. Our study was limited by a small sample size of 50 patients. In order to prove the difference between the two groups at significance level 0.05 with 80% power, we determined that 745 patients would be needed in each group. Furthermore, we recognize that testosterone deficiency did not uniquely correlate with characteristics of priapism history such as episode frequency, number, and duration in our study cohort; however, there was a trend towards the association of priapism history and free testosterone levels. Additionally,

only a single early morning level of testosterone was measured. Due to the daily fluctuations in testosterone levels, two or more averaged reading would have been preferred. Although we excluded several conditions affecting testosterone levels, we acknowledge that other unassessed variables such as liver disease or exercise may affect testosterone levels. A possible concern with this study is our use of a total testosterone cut-off value of 12 nmol/L to indicate testosterone deficiency. It is important to note that testosterone reference values are based on statistical analyses of a wide population of subjects including older men. Consequently, utilizing this cut-off in a sample of mostly younger men may be a limitation because of a possible underestimation of the extent of testosterone deficiency. Finally, we did not measure bioavailable testosterone which may have provided a more accurate representation of deficiency.

CONCLUSIONS

Testosterone deficiency and priapism are both common phenomena that occur among the SCD population. Unfortunately, we were unable to satisfactorily demonstrate an association between the two. Though treatment is recommended for symptomatic men with low testosterone levels, testosterone replacement therapy (TRT) is avoided in men with SCD due to the fear of inducing priapism. In allaying these fears, we recently demonstrated that TRT does not induce episodes of priapism in men with SCD [29]. We believe that if rigorous trials prove TRT to be effective in preventing or reducing stuttering priapism episodes in the SCD population, this intervention could offer a safer therapeutic option with dual actions. Further studies are warranted to evaluate the natural history and clinical correlates of priapism occurrences in SCD patients with and without testosterone deficiency that may more precisely reveal risk associations. Additional investigation to identify the molecular mechanisms by which testosterone deficiency occurs and contributes toward priapism in SCD is also worthy of support.

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Table 1

Baseline Priapism History Characteristics (n = 24)

Priapism History Characteristics	Frequency (%)
Age of onset of priapism (years)	
13–17	36
18–25	59
>25	5
Precipitating activity	
Sleep	95
Intercourse	5
Frequency of priapism episodes	
Daily	9
Alternate days	14
Once weekly	18
Once monthly	14
Other	45
Duration of priapism episodes	
<30 min	41
1 hour	32
2 hours	9
2–5 hours	9
>5 hours	9

Table 2

Laboratory Values of Patients with Priapism

Variable (Normal Range)	Mean (SD) in Patients with Priapism	Mean (SD) in Patients without Priapism	P Value
Age (years)	32.6 (1.7)	35.8 (1.7)	0.21
Haemoglobin (Hb) (14.0–18.0 g/dl)	7.8 (1.8)	7.9 (1.8)	0.83
Luteinizing hormone (LH) (0–25 IU/L)	7.4 (2.3)	8.1 (2.4)	0.57
Follicle stimulating hormone (FSH) (0–20 IU/L)	7.2 (4.6)	7.2 (4.8)	0.97
Total testosterone (12.5–38.1 nMol/L)	16.7 (4.9)	15.4 (5.9)	0.43
Free testosterone (194.4–936.1pMol/L)	327.0 (135.3)	287.8 (108.0)	0.26

SD = Standard Deviation

Table 3

Association Between Testosterone and Priapism

Total Testosterone	History of Priapism n (%)	No History of Priapism n (%)	Total n (%)	P Value
12 nmol/L	5 (19.2)	6 (25.0)	11 (22.0)	0.623
>12 nmol/L	21 (80.8)	18 (75.0)	39 (78.0)	
Total	26 (52.0)	24 (48.0)	50 (100)	

n = Number