ORIGINAL ARTICLE

Risk factors for hypogonadism in young men with erectile dysfunction

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Abstract

Background: The objective of this study is to evaluate the hormone profile of young men with the chief complaint of erectile dysfunction (ED) and determine the comorbidities in this population.

Methods: A retrospective chart review of men aged 18 to 40 years who presented with ED and had a hormone evaluation but without prior medication for hormone manipulation from 2002 to 2016 was performed at a tertiary care institution. Data were obtained on demographics, comorbidities, medications, and hormonal evaluations.

Results: A total of 2292 men with ED were identified and 2130 of them received testosterone level evaluation. The most common comorbidities that men were actively being treated for were depression (22.3%), anxiety (16.1%), hypertension (15.6%), diabetes (7.2%), cancer (6.2%), and cardiovascular disease (3.3%). The average total testosterone level was 368 ± 160 ng/dL; 10.7% of men had hypogonadism. Multivariate analysis demonstrated age, body mass index (BMI), depression, and cancer predicted a hypogonadal status. Patients with BMI > 28.2 kg/m^2, age > 34 years, cancer diagnosis, or depression were 3.350-fold, 1.447-fold, 2.317-fold, or 1.420-fold more likely to be diagnosed hypogonadal than nonoverweight, age ≤ 34 years, noncancer, or nondepressive patients.

Conclusion: The majority of men under the age of 40 with ED exhibit a normal hormonal milieu. Young ED men with BMI > 28.2 kg/m^2, age >34 years, cancer diagnosis, or depression are at risk for hypogonadism.

Keywords: Erectile dysfunction; Hormone; Hypogonadism; Men

1. INTRODUCTION

Erectile dysfunction (ED) is an increasing common complaint as men age, with >70% of men aged 70 years and older complaining of ED. However, even in <40-years-old men, the rates of ED are reported to be >5%.[1] Many medical comorbidities have been attributed to ED, such as cardiovascular disease or diabetes, with the prevalence of these comorbid conditions also rising with increasing age. Additionally, many medications used to treat these conditions, such as antihypertensives, have been independently associated with ED as well. The incidence of many of these more classical ED-associated co-morbidities is much lower in younger men, pointing to the potential larger contribution of different etiologies of ED in this cohort. Other potential etiologies include things such as anxiety or other psychiatric disorders.[1]

Hypogonadism, or low testosterone, has also been attributed as a risk factor for ED. It is known that androgens are necessary for an adequate erectile response.[2] Studies support the benefit of testosterone on erectile function in hypogonadal men; however, many of these studies such as the Testosterone Trial were performed in older men.[3] The prevalence of hypogonadism and other hormonal abnormalities in younger men presenting with ED is poorly understood. Additionally, many of the symptoms of hypogonadism are vague and can overlap with many other comorbid conditions. In this study, we aim to better define the hormonal profile of young men presenting with ED and to obtain information on other potential contributing factors for ED such as comorbidities and medications. We hypothesized that the majority of young men with ED will have normal hormonal levels.

2. METHODS

2.1. Subjects

Institutional Review Board approval was obtained to perform a retrospective chart review to identify men aged 18 to 40 years who are sexually active and presented to the clinic at our tertiary care institution from 2002 to 2016 with the complaint of ED and had a hormonal evaluation but without prior medication

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for hormone manipulation. This hormonal evaluation included testing for total testosterone (T), prolactin (Pr), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels. This search was performed using the Northwestern Enterprise Data Warehouse, an integrated repository of all clinical and research data from Northwestern University Feinberg School of Medicine and Northwestern Memorial HealthCare. Data were obtained on patient demographics, comorbidities, medications, hormonal evaluations, and treatments given for ED. Data were screened to ensure comorbidities and medication use were active at the time of clinical evaluation for ED and the hormonal evaluation.

If men had multiple hormonal evaluations, only the first values obtained during the evaluation of ED were considered.

The following definitions were used for normal laboratory values: T level > 200 ng/dL, Pr level < 13.1 ng/mL, LH level 1.2 to 9.0 mIU/mL, and FSH level 1.3 to 19.3 mIU/mL.

2.2. Statistical methods

The Chi-square test is used to compare relationships between categorical variables and the Student's *t*-test was used to analyze continuous variables. Receiver operating characteristic (ROC) curves were used to determine the appropriate cut-off value for age and BMI to discriminate hypogonadal from eugonadal subjects. Cut-off value for age and BMI, along with variables that were statistically different for ED patients with or without hypogonadism, were included in the multivariable analysis. p values less than 0.05 were considered statistically significant.

3. RESULTS

A total of 2292 men were identified who met the inclusion criteria. The average age was 32.7 years (SD 5.1). ED was more commonly reported in older men in the cohort, with 35.2% of the men being aged 36 to 40 years compared to 9.6% being aged 18 to 25. In terms of racial demographics, the most prevalent identification was White at 42.9%. Average body mass index (BMI) was 28.1 kg/m^2 (SD 5.8). Demographic data are summarized in Table 1.

Many men reported comorbid conditions, which have been associated with ED. The most common comorbidities were depression (22.3%), anxiety (16.1%), hypertension (15.6%), diabetes (7.2%), cancer (6.2%), and cardiovascular disease (3.3%). Leukemia, lymphoma, and testicular cancer patients comprise majority of cancer patients in our cohort. Comorbidity and medication data are also summarized in Table 1.

The results of the hormonal evaluations that were performed in young men with ED are summarized in Fig. 1. A testosterone level was obtained in 2130 men. The mean T level was 368 ng/dL (SD 160 ng/dL) with a median T of 345 ng/dL. Hypogonadism (T < 200 ng/dL) was found in 10.6% of men while 89.4% of men had a normal T level. A prolactin level was obtained in 2216 men. The mean Pr level was 9.3 ng/mL (SD 34.7 ng/mL) with a median Pr of 7.8 ng/mL. A normal Pr level was present in 91.5% of men while 8.5% had hyperprolactinemia. LH and FSH levels were checked in 923 and 866 men, respectively. Abnormalities in LH levels were found in 10% of men; 9.1% of men had an abnormal FSH level.

A total of 2130 men with testosterone level were analyzed. Age, BMI, and a number of comorbidities were related to young ED men with hypogonadism. Univariate analysis demonstrated depression, hypertension, cancer, diabetes, cardiovascular disease, and peripheral vascular disease were significantly more frequent in hypogonadal patients than in eugonadal patients (Table 2). ROC curve analysis determined the cut-off value of age as 34 years and BMI as 28.2 kg/m^2 to better discriminate hypogonadal from eugonadal subjects. In multivariate analysis including all significant variables, only depression, cancer, age, and BMI predicted a hypogonadal status. Of note, patients with BMI > 28.2 kg/m^2, age > 34 years, cancer diagnosis, or depression were 3.350-fold, 1.447-fold, 2.317-fold, or 1.420-fold more likely to be diagnosed hypogonadal than nonoverweight, aged ≤ 34 years, noncancer, or nondepressive patients (Table 3).

Five out of 51 HIV men were hypogonadal, but presence of HIV did not identify men with testosterone levels < 200 ng/dL (p = 0.842). Seven hypogonadal ED subjects and 85 eugonadal ED subjects receive HIV medication for either treatment or prevention, but HIV medication was also not associated with hypogonadism (p = 0.333). Testosterone levels, however, are higher in 51 HIV men compared to 2079 non-HIV subjects (mean testosterone level 436.4 ± 246.5 ng/dL vs 366.6 ± 157.3 ng/dL, p = 0.002). A total of 22% of the cohort endorsed recreational usage of marijuana and all of them denied on illicit drug use. Serum testosterone did not differ between marijuana usage subjects and nonmarijuana usage subjects (mean testosterone level 358.7 ± 162.3 ng/dL vs 371.2 ± 159.6 ng/dL, p = 0.128).

The majority of young men (2138 or 93.3%) with ED were given pharmacological treatments for their ED (Fig. 2). The most common treatment given was a phosphodiesterase 5 inhibitor (PDE5i) in 68.7% of men. Testosterone was given to 12.9% of men and 6.7% received either nonpharmacologic or no treatment for ED.

Table 1

Demographic characteristics of the patients with erectile dysfunction

Characteristics	Patients (n = 2292)
Age, y	
Mean (SD)	32.7 (5.1)
Median	33
BMI, kg/cm^2	
Mean (SD)	28.1 (5.8)
Median	26.8
Testosterone, ng/dL	
Mean (SD)	368 (160)
Median	345
Comorbidities, n, %	
Anxiety	368 (16.1)
Depression	510 (22.3)
Hypertension	357 (15.6)
Cancer	141 (6.2)
HIV	58 (2.5)
Diabetes	166 (7.2)
Hemiplegia/paraplegia	41 (1.8)
Cardiovascular disease	75 (3.3)
Peripheral vascular disease	46 (2.0)
Medications, n, %	
NSAIDs	668 (29.1)
Antihypertensive	357 (15.6)
Antidepressant	510 (22.3)
Antianxiety	368 (16.1)
Muscle relaxant	212 (9.2)
Antihistamine	174 (7.6)
H2-receptor antagonist	139 (6.1)
Antiepileptic	86 (3.8)
Antipsychotic	84 (3.7)
Anti-HIV medication	94 (4.1)
Marijuana usage	504 (22.0)

BMI = body mass index; HIV = human immunodeficiency virus; NSAID = nonsteroidal anti-inflammatory drug.

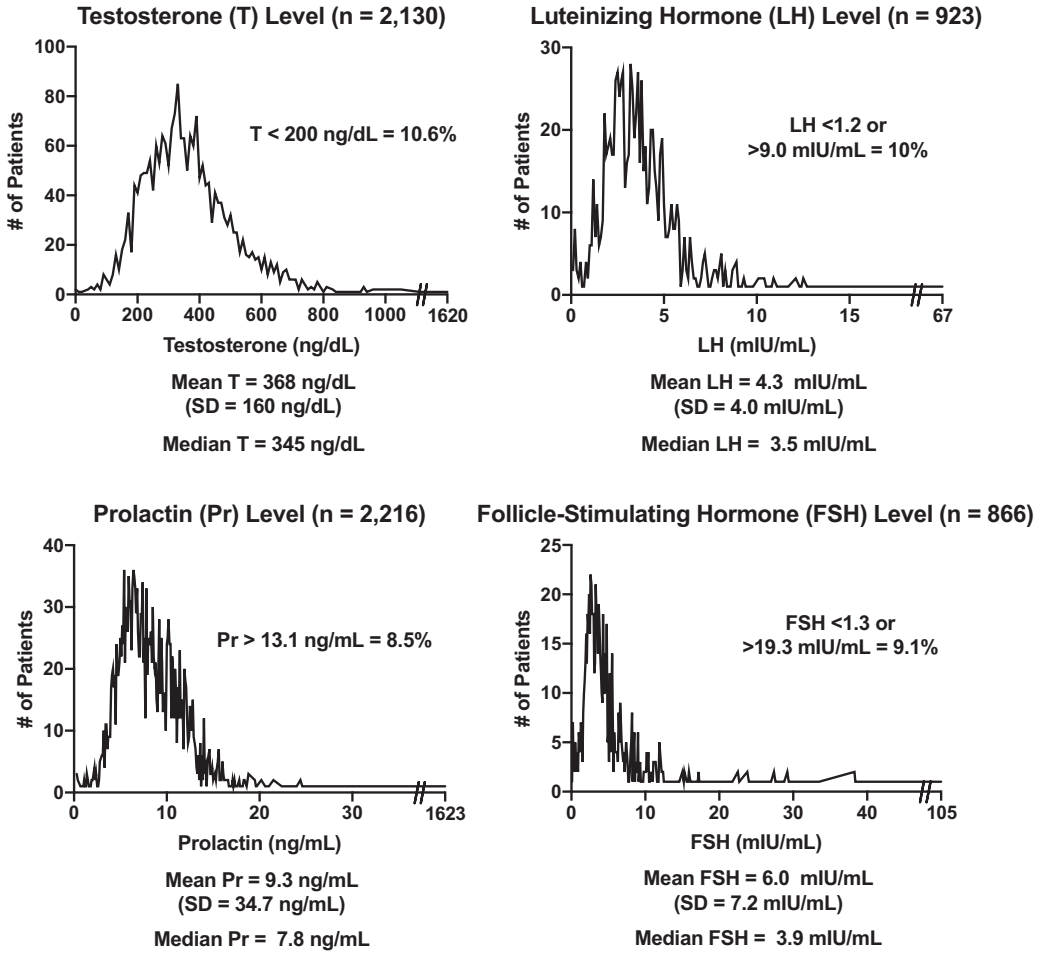

Fig. 1 Hormonal profiles of young men with erectile dysfunction (ED).

4. DISCUSSIONS

4.1. Diagnosis of hypogonadism based on serum testosterone level

This study demonstrated that a majority of young men (aged 18 to 40 years) with ED have normal hormonal profiles. Using a cut-off value < 200 ng/dL, 10.6% of men were identified as hypogonadal. While there is no consensus on the T level below which hypogonadism should be defined, the International Society of Andrology (ISA), the International Society for Study of the Aging Male (ISSAM), the European Association of Urology (EAU), the European Association of Andrology (EAA), and the American Society of Andrology (ASA) recommended total testosterone level below 230 ng/mL (with hypogonadism symptoms) may require testosterone treatment. However, total testosterone level between 230 and 350 ng/mL will require further measurement of free testosterone to determine the biochemical diagnosis of hypogonadism.[4] Instead of using 230 ng/mL as a cut-off value for diagnosis of hypogonadism, threshold of 200 or 300 ng/mL is otherwise suggested by different organization guidelines.[5,6] In our study, while the total testosterone level was checked from the time of the visit, a value of <200 ng/dL is on the conservative end of proposed values, concerning the diurnal change of testosterone. Following circadian rhythm, a minimal fall of 43% is suggested from peak to nadir, by this manner one can predict the peak total testosterone level can be 350 ng/mL if nadir of 200 ng/mL is observed.[7] If a more liberal criteria of <300 ng/dL were used, then 35% of men in this study would be considered hypogonadal. Abnormalities of other hormones such as prolactin, FSH, and LH were less common. We do, however, offer FSH, LH, and prolactin check-up for patients with not only ED but also fertility concern.

Table 2

Characteristics of ED patients with hypogonadal and eugonadal status

	Hypogonadal (n = 227)	Eugonadal (n = 1903)	*p*
Age, y	34.5 ± 4.7	32.6 ± 5.0	**<0.001**
BMI, kg/cm^2	31.7 ± 7.7	27.6 ± 5.3	**<0.001**
Testosterone, mg/dL	153.6 ± 42.3	393.7 ± 149.7	**<0.001**
Comorbidities, n, %			
Depression	66	409	**0.009**
Anxiety	45	300	0.117
Hypertension	59	280	**<0.001**
Cancer	28	106	**<0.001**
HIV	5	46	0.842
Diabetes	32	126	**<0.001**
Hemiplegia/paraplegia	2	32	0.573
Cardiovascular disease	13	38	**<0.001**
Peripheral vascular disease	9	33	**0.022**

Bolded significance values indicate $p < 0.05$.

Table 3

Multivariate logistic analyses of comorbidities predicting hypogonadism

Characteristics	Odds ratio	95% CI	*p*
Depression	1.420	1.004-2.009	**0.048**
Hypertension	1.104	0.740-1.648	0.629
Cancer	2.317	1.425-3.766	**0.001**
Diabetes	1.363	0.839-2.214	0.211
Cardiovascular disease	1.427	0.676-3.013	0.351
Peripheral vascular disease	1.443	0.621-3.354	0.394
Age > 34 y	1.447	1.072-1.952	**0.016**
BMI > 28.2 kg/m^2	3.350	2.454-4.572	**< 0.0001**

Bolded significance values indicate $p < 0.05$.

4.2. Etiology of ED

The causes of ED have been stratified into psychogenic, organic, or combined as originated; nevertheless, diagnosis of psychogenic ED is often given for patients who presented to clinic under the age of 40, based on the concept of organic ED as an age-dependent disease, regardless of the multifactorial pathogenesis of ED.[8] In a multinational study involving 13 342 men under the age of 40, 10% of men were diagnosed with ED. The results were consistent with other studies with prevalence of young ED patient range from 5% to 30% and the majority of the subjects being diagnosed with the primary etiology of psychogenic related in this population.[9–13] In addition to the conceptual perspective of psychological origin in the young ED patients, organic aspect including metabolic, endocrine, vasculogenic, and neurologic condition should also be considered as causes for a thorough understanding of patients' condition.

4.3. Cardiovascular disease in young ED patients

The importance of early diagnosis for young ED patients should not be over-emphasized. ED could serve as a sentinel symptom of early vascular disease or subclinical endothelial dysfunction related to diabetes, hypertension, and metabolic syndrome.[14] Based on the theory by Montorosi and colleagues, due to the narrow caliber of penile artery, penile circulation may be compromised in early stage of atherosclerosis, presenting itself as an ED complaint.[15] The marked increase in future cardiovascular risk for young ED patients reminds us, although only 3.3% of young patients with ED is identified with cardiovascular disease in our cohort, care should be taken and potential cardiovascular hazard need to be addressed. Hypertension and diabetes account for 15.6% and 7.2% in our study, which is higher than previous research reporting percentage of 12% and 6.7%.[16] These two factors have been identified as risk factor for young ED patients, suggesting endothelial dysfunction as an underlying mechanism for ED can exert clinical symptoms in the early stages. It is also well known that HTN, cardiovascular disease, and diabetes are associated with ED. Not surprisingly, this cohort demonstrated appreciable rates of these conditions. Similar to the psychiatric conditions, there was a higher prevalence of these conditions among this cohort than in population based on studies of men of similar age.[17] Again, this may point to the possible contribution of these comorbidities to the etiology of the ED.

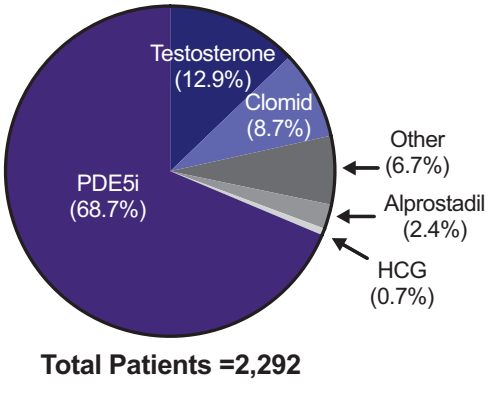

Fig. 2 Treatments given for erectile dysfunction (ED).

4.4. Hormone manipulation for young hypogonadal ED patients

In general, serum testosterone declines after age 40, at the rate of 0.4% to 1.6% per year.[18,19] By using the definition of total testosterone < 200 ng/mL, 10.6% of men in our study fulfilled the criteria of hypogonadism, which is uncommon in young population. A similar percentage of elevated and declined gonadotropin is observed, clarifying both primary gonadal failure and secondary hypogonadism are responsible for the hormone abnormality. The etiology of young hypogonadal men includes Klinefelter syndrome, congenital hypogonadotropic hypogonadism, acquired hypogonadotropic hypogonadism, and cryptorchidism. Klinefelter syndrome represents the most common chromosomal disorders occurring in one or two cases in every 1000 live births.[20] Although with a broad spectrum of phenotypical appearance, a majority of subjects are hypogonadal associated with infertility and regarded as risk factor for ED. Prevalence of severe ED in Klinefelter syndrome patient is estimated from 2.5 to 22.7% in different age range from different studies. Interestingly, hypoactive sexual desire was found to be associated with the syndrome compared with testosterone-matched control instead of ED.[21–23] The treatment of hypogonadism in men with testosterone for ED, especially young men, needs to be undertaken with some consideration. Exogenous testosterone supplement is regarded as a contraceptive method by exerting negative feedback on the hypothalamic–pituitary axis as endogenous testosterone in a dose- and duration-dependent fashion.[24] Younger men may be more likely to have fertility concerns as well, and must be counseled on the potential impact of testosterone replacement on their fertility potential. For men who desire and maintain future fertility, alternative treatment options, which stimulate testicular testosterone production, such as hCG and clomiphene citrate are recommended. In our study, 12.9% of men received testosterone treatment, although only 10.6% of men fit in the definition of hypogonadism, which leads to the questioning of overtreatment in our cohort. As a matter of fact, testosterone replacement therapy for young hypogonadal men is not an absolute contraindication as long as they have symptoms associated with low testosterone and accept infertility as a possible consequence.

4.5. HIV and ED

While focusing on the organic cause of ED in young patients, treatment should start with great caution to rule out HIV infection if the patient has known or suspected to have specific behavioral risk for infection. Endocrinological disorders are common in patients with HIV infection, and hypogonadism related to HIV is possibly related to inflammation of gonadal axis or direct gonadal infiltration with HIV or opportunistic agent.[25] Although direct link between HIV and ED remains poorly understood, the frequencies of ED are significantly higher in the HIV-infected population. Underlying condition including depression, anxiety, psychological stress, illicit drug use, and metabolic syndrome can all be the causes.[26,27] Deterioration of metabolic pattern that promotes endothelial dysfunction contributed to highly active antiretroviral therapy (HAART), the treatment for HIV, may

also be a factor associated with ED.[28,29] To our surprise, the serum testosterone levels in HIV patients with ED are higher than in non-HIV men with ED, but the hypogonadism prevalence and serum testosterone concentration were comparable to the previous study that enrolled 1325 HIV male patients.[30] This suggested other contributing factors in our cohort have greater impact on the testosterone level in young ED men other than HIV infection.

4.6. Limitations of the study

Although the research enrolled large number of young men with ED, there are some unavoidable limitations. First, this study is limited by its retrospective design. Additionally, while men reported their current medications at the time of the visit, we cannot verify the accuracy whether these medications were being taken or taken properly. Moreover, we are not able to have the information about the severity of ED, depression, anxiety, social status, and history of smoking or drinking, to evaluate the impact on these confounding factors. Lastly, testosterone levels were total testosterone levels from the time of the visit and were not necessarily AM levels.

In conclusion, the majority of men <40 years of age with ED exhibit a normal hormonal milieu. Given the low specificity of signs and symptoms of androgen deficiency in ED patients, a clinical diagnosis of ED in men under the age 40 with BMI > 28.2 kg/m^2, age >34 years, cancer diagnosis, or depression should trigger an evaluation of patients' testosterone level.

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