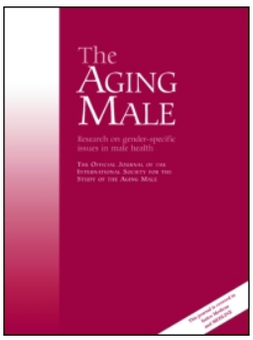

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ORIGINAL ARTICLE

Serum testosterone status in men with penile corporoveno-occlusive dysfunction

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ABSTRACT

Background and objectives: Vascular abnormalities are the most common factors in patients with erectile dysfunction (ED). There are limited number of case series investigating the etiology of corporoveno-occlusive dysfunction (CVOD). In this study, we evaluated ED patients with vascular etiologies and their serum biomarkers from a large database.

Materials and methods: The current study retrospectively examined the association between serum testosterone levels and basic lab works with Penile Doppler Ultrasonography (PDU) results. We retrieved and reviewed the records of 500 ED patients who had PDU at our institution between January 2012 and November 2018. One-way analysis of variance and Pearson's correlation coefficients were used to compare different parameters between groups (CVOD and penile arterial insufficiency) and between two quantitative variables, respectively.

Results: Sixty patients who met the inclusion criteria were enrolled and examined in this study. Patients' mean age was 52.9 ± 11.5 years, and mean serum testosterone level was 15.57 ± 6.49 nmol/L. Thirty-nine (65%) out of 60 patients had abnormal EDV values (>5cm/sec), while eleven (18.3%) had abnormal PSV values (<35cm/sec). Among the patients with abnormal EDV values, we demonstrated that there was a statistically significant negative correlation between testosterone and CVOD (Pearson's; $r = -0.283$; $p = .028$).

Conclusions: Our findings supported that low serum testosterone level is a risk factor for CVOD and so for ED. Future studies would benefit from larger sample sizes in order to support or refute our findings.

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corporoveno-occlusive dysfunction; erectile dysfunction; penis; testosterone

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a sufficient erection to engage in sexual intercourse. Vascular abnormalities are the most common factors in patients with an organic etiology of ED [1]. There is no doubt that arterial inflow and sinusoidal relaxation are important in the erectile phenomenon, however, failure to trap cavernosal blood within the corpora cavernosa is a common cause of ED [2].

In 1980, Virag, a cardiovascular surgeon specialized in andrology, clearly stated that "vasculogenic ED does exist" and introduced using PDU in the investigation of ED [3]. Later, Virag exposed to the literature the ability of an intracavernosal injection of papaverine to induce an erection [4]. Extraordinarily, an accidental intracavernosal injection of that drug during an arterial epigastric cavernous anastomosis was the reason behind the new dimension in diagnosis and intracavernosal injection treatment [4].

Penile corporoveno-occlusive dysfunction (CVOD), which is synonymous with venous leakage/insufficiency and venogenic ED, represents the most common vascular dysfunction [5], and can be identified in up to 85% of men evaluated for ED, regardless of the age of the patient [5–7]. Most patients with vascular ED are in this group, however, a minority of especially younger patients may develop ED because of circumscribed acquired or congenital vascular abnormalities.

The effect of androgens on the physiology of the penis has been a topic of discussion for many years. In animal models, testosterone has been shown to effect the architectural integrity of penile smooth muscles [8]. After introduction of sildenafil, which is the first introduced phosphodiesterase type 5 inhibitor (PDE5i) to the market in treating ED, basic and clinical studies were accelerated to understand the pathophysiology of ED. In a laboratory study, Traish et al. demonstrated that androgen deprivation alters the

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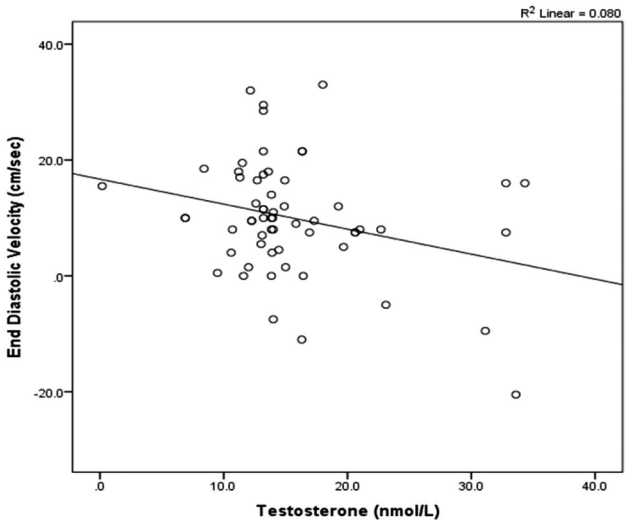

Figure 1. Correlation between end diastolic velocity and total testosterone.

functional responses and structure of erectile tissue [9]. In the following years, scientists concentrated on patients treated for ED who did not respond well to PDE5i medicines [10]. Accordingly, Aversa et al. investigated the role of androgens in regulating trabecular smooth muscle relaxation in the corpus cavernosum in response to vasoactive challenge in men with ED [11]. The latter study results indicated that low testosterone may correlate independently of age with the impaired relaxation of cavernous endothelial and corporeal smooth muscle cells to a vasoactive challenge in men with ED [11]. These findings gave clinical support to the experimental knowledge of the importance of androgens in regulating smooth muscle function in the penis. Also, several follow up human studies showed that testosterone replacement therapy in hypogonadal men can improve erectile function in patients with CVOD [12–16]. Although earlier studies' results are fascinating, there was no other study on this topic investigating the etiology of CVOD.

In the etiology of ED, a great percentage of the patient population undergoing penile prosthesis implantation are having vascular factors including CVOD. We aim in this study to give a standpoint to CVOD patients whether they have hypogonadism or not.

Patient and methods

Ethics, sample and setting

This retrospective study was undertaken at the urology department of a tertiary teaching hospital and was approved by the Medical Research Centre of the institution (Protocol #: MRC-01-18-135). Search for data was retrieved from the medical records of all patients who underwent penile Doppler ultrasonography (PDU) (in between January 2012 and November 2018) for evaluation of ED.

The main eligibility criterion of the current study was patients with PDU, and all those eligible were included in the study. The exclusion criteria included known pituitary, testicular or adrenal diseases; current use of medications that affect pituitary and testicular functions or a clearance of sex steroids (any hormones e.g. testosterone, dehydroepiandrosterone, anti-androgens, a GnRH agonists) immune disorders and immunosuppressive therapy.

We entered the data of PDU results of ED patients from the last 6 years' records to an excel sheet. The following data was extracted from the records of patients for cholesterol (mmol/L), Vitamin D (ng/mL), total testosterone (nmol/L), mean peak systolic velocity (PSV) (cm/s) and end diastolic velocity (EDV) (cm/s) from the PDU investigations.

Statistical analysis

All Statistical analyses performed using SPSS 23.0 (SPSS Inc. Chicago, IL, USA) and Epi-info (Centers for Disease Control and Prevention, Atlanta, GA) statistical softwares, with p set at $<.05$. Quantitative data were expressed as frequency and percentage or mean ± SD and range. Descriptive statistics summarized the sample's demographic and other clinical characteristics.

One-way analysis of variance (ANOVA) was used to compare different parameters (such as PSV and EDV) between three groups (normal, CVOD, arterial insufficiency according to PDU study results). Relationships between two quantitative variables (e.g. testosterone and PSV, etc.) were examined using Pearson's correlation coefficients.

Results

Medical records of a total of 500 ED patients were retrieved during the study period, which included all patients with PDU investigation, and all those eligible patients were included in this study.

Mean age was 52.9 ± 11.5 years old and mean serum testosterone level was 15.57 ± 6.49 nmol/L. About 65% (39/60) of the patients had EDV values >5cm/sec, and 18.3% (11/60) had PSV values <35cm/sec.

Among the patients with EDV values, there was a significant negative correlation between testosterone and CVOD (Pearson's; $r = -0.283$; $p = .028$) (Figure 1). Among the patients with PSV values, there was

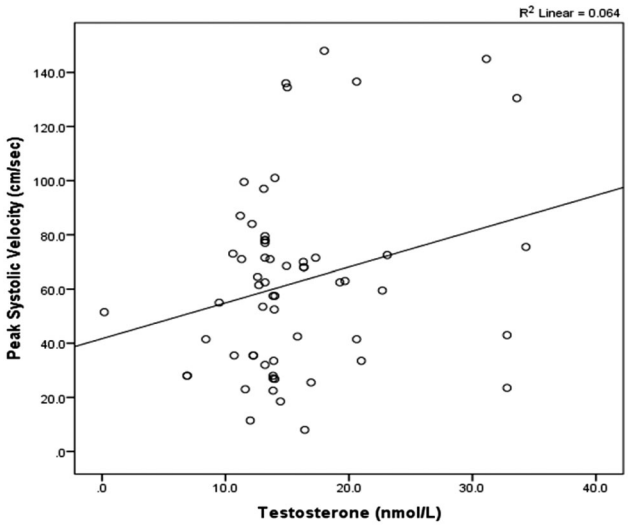

Figure 2. Correlation between peak systolic velocity and total testosterone.

positive correlation between testosterone and arterial insufficiency, however, it did not reach statistical significant (Pearson's; $r = 0.252$; $p = .052$) (Figure 2, Table 1).

Discussion

ED affects physical and psychosocial health and significantly impacts the quality of life of men and their partners. It is uncommon in young men, but more common in middle age, and is highly prevalent in men aged $>$ 60 years. Thus, to some extent, ED is a natural expression of aging. Oftentimes a treatment plan can be formulated after a focused history, physical exam and basic lab-work are conducted. The current study examined the association between serum testosterone levels and the outcome of the PDU results of sixty men with ED. This study demonstrated that there is a negative correlation between CVOD and serum testosterone levels. This negative relation was significant and low serum testosterone levels was a risk factor for CVOD and so for ED.

In the last decades of twentieth century, scientists investigated what they can do for ED. When the first results of penile deep dorsal vein ligation were published to treat CVOD [17], surgeons were motivated since there was a surgical treatment of a curable cause of ED. Later, plentiful techniques (e.g. deep dorsal vein ligation/excision [18,19], crural plication/ligation [20]) were published, but inclusion criteria, patient selection, and success evaluation differed extremely between study groups. Meanwhile, studies revealed that in patients who had ED due to CVOD, resection of the deep dorsal vein of the penis could provide a transient satisfactory result, and should not be considered as a long-term treatment modality [18,19,21]. Their data suggested that venous surgery should only be offered to a selected group of patients comprising young ED patients with CVOD [21,22]. Old age, neurogenic disorders causing ED, and diabetes mellitus were the main exclusion criteria for CVOD surgery [19,21,22].

Unfortunately, most methods of penile venous surgery were invented before basic research defined the pathophysiologic mechanisms of CVOD [15]. In most patients CVOD is the result of endothelial dysfunction and damage to the trabecular smooth muscle content due to multifactorial degenerative processes [2]. Decreased cavernosal smooth muscle mass may impair erectile function. Its association with ED originated from CVOD may be a poor prognostic factor of the outcome of surgical therapy [23]. These structural alterations will not be affected by surgical ligation of extracorporeal venous outflow. According to latest urology guidelines, penile venous surgery is not recommended because of the lack of compelling evidence that it constitutes an effective ED management strategy in most men [24]. Randomized trials of men who underwent various versions of penile venous ligation surgery indicate that such surgery is unlikely to result in long-term successful management of ED for the overwhelming majority of men and delays treatment with other more reliable options such as penile prosthesis surgery. Today it is agreed by most, that venous leakage is an effect rather than a cause [25].

It is known, mainly from animal experiments, that androgens influence the function of vascular and non-vascular smooth musculature [26]. Although the exact role of androgens in erectile function in men is controversial, primary or secondary hypogonadism is considered key in the pathophysiology of ED [27–29]. Androgens exert not only genomic effects, e.g. stimulate the expression of the neuronal isoform of nitric oxide synthase [30,31], but also non-genomic effects, e.g. relax on the smooth musculature of coronary arteries and the aorta [32,33].

Limited number series of case reports also suggested that testosterone therapy improves erectile function in hypogonadal men by restoring veno-occlusive function in patients with penile CVOD [12,13]. In one of the earliest papers, Yassin et al. presented case reports of hypogonadal men ($N = 12$) with low plasma testosterone and moderate to severe ED [13]. In the latter study, co-morbidities varied, including diabetes mellitus type I or II, metabolic syndrome with possible

Table 1. Clinical characteristics, blood results and PDU findings of patients.

	Arterial insufficiency (PSV $\leq$ 35 cm/sec)	CVOD (EDV $\geq$ 5 cm/sec)	Normal	*p*-Value
Age (years)	56.5 ± 9.5	52.7 ± 11.4	49.3 ± 13.6	.368
Testosterone (nmol/L)	13.8 ± 3.7	11.3 ± 6.5	18.4 ± 8.3	.247
Vitamin-D (nmol/L)	22.7 ± 7.1	27.1 ± 13.6	31.4 ± 15.5	.320
Cholesterol (mmol/L)	4.4 ± 1.0	5.8 ± 6.1	8.9 ± 13.7	.415
PSV average (cm/sec)	24.2 ± 8.9	67.5 ± 29.1	83.7 ± 39.0	.000
EDV average (cm/sec)	5.5 ± 3.8	14.7 ± 7.2	−3.8 ± 8.6	.000

CVOD: corporoveno-occlusive dysfunction; PSV: peak systolic velocity; EDV: end diastolic velocity.

related hypertension, dyslipidemia, or obesity. In another case series study, Kurbatov et al. recruited 29 patients with ED (age range 32–65 years), with low plasma testosterone, who did not respond to phosphodiesterase type 5 inhibitor therapy [12]. Kurbatov et al. employed PDU as objective criteria to evaluate penile arterial and venous blood flow. Moreover, pharmaco-cavernosography was carried out in 9 patients and magnetic resonance imaging with intracavernosal contrast enhancement was carried out in 8 patients for confirmation of diagnosis of CVOD. Kurbatov and colleagues suggested that, testosterone therapy improves venous leakage in hypogonadal men with ED [12]. Latest literature supported long-term testosterone therapy and showed that it alleviates ED, improves cardiometabolic risk factors, and reduces prostate cancer [34].

In a recent meta-analysis study, Corona et al. investigated the effect of testosterone treatment on sexual function by performing a meta-analysis on 14 articles which enrolled 2,298 participants [35]. Corona et al. demonstrated that testosterone treatment significantly improves ED, as well as other aspects of sexual function, in men with testosterone deficiency [35]. One of the important result of the latter study was about patients with more severe hypogonadism (total testosterone $<$8 nmol/L), because the authors reported greater changes in final erectile function score when compared with those with a milder testosterone deficiency [35].

Our study has limitations. On one hand it is retrospective in nature and does not have the profound significance similar to prospective or randomized controlled studies. This suggests that a larger scale studies are necessary to define outcomes.

Conclusion

Our findings supported that low serum testosterone level is a risk factor for CVOD and so for ED. Future studies would benefit from larger sample sizes in order to support or refute our findings.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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