FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Mariana Marques Martins Santiago

Hormone levels and Peyronie's disease: more than testosterone deficiency?

março, 2014

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Mariana Marques Martins Santiago

Hormone levels and Peyronie's disease: more than testosterone deficiency?

Mestrado Integrado em Medicina

Área: Urologia

Trabalho efetuado sob a Orientação de:

Professor Doutor João Nuno Tomada Marques

Trabalho organizado de acordo com as normas da revista:

The Journal of Sexual Medicine

março, 2014

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Mariana Marques Martins Santiago, abaixo assinado, nº mecanográfico 200802331, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 18/03/2014

Assinatura conforme cartão de identificação:

Mariana Marques Martins Santiago

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME
Mariana Marques Martins Santiago

CARTÃO DE CIDADÃO	E-MAIL	TELEMÓVEL
13831351	mimed08162@med.up.pt	918574751

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
200802331	Julho 2014

DESIGNAÇÃO DA ÁREA DO PROJETO
Urologia

TÍTULO DA DISSERTAÇÃO
Hormone levels and Peyronie's disease: more than testosterone deficiency?

ORIENTADOR
Professor Doutor João Nuno Tomada Marques

É autorizada a reprodução integral desta Dissertação/Monografia (riscar o que não interessa) para efeitos de investigação e de divulgação pedagógica, em programas e projectos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 18/03/2014

Assinatura conforme cartão de identificação: Mariana Marques Martins Santiago

Letter to the Editor

To the attention of:
Irwin Goldstein, MD
Editor-in-Chief of « The Journal of Sexual Medicine »
Department of Sexual Medicine, Alvarado Hospital
University of California
San Diego, CA USA

Oporto, March 18th, 2014

Dear Mr. Irwin Goldstein:

Please accept the submission of the research article entitled:

« Hormone levels and Peyronie's disease: more than testosterone deficiency? »

The mailing address is:

Mariana Marques Martins Santiago
Rua Afonso Baldaia, nº 775
bloco 781, apart. 341
4150-018
Oporto, PORTUGAL
mariana_santiago_3@hotmail.com Tel. +351918574751

The guarantor is myself, address above.

I herewith declare that all authors, Mariana Santiago, Nuno Tomada and Francisco Botelho, have agreed upon this submission.

Furthermore, I declare that the paper is not currently being considered for publication by another journal, and, if accepted, it will not subsequently be published in the same or similar form in any language without the written consent of the publisher.

Thank you for your attention,

Warm regards,

Mariana Santiago, MD

Supplementary file not for review

Hormone levels and Peyronie's disease: more than testosterone deficiency?

Mariana Marques Martins Santiago, MD; Faculty of Medicine of Porto University, Porto, Portugal; mariana_santiago_3@hotmail.com

João Nuno Tomada Marques, MD, PhD; Department of Urology of S. João Hospital; Faculty of Medicine of Porto University; Institute for Molecular and Cell Biology of Porto University (IBMC), Porto, Portugal;

Francisco Botelho, MD; Department of Urology, Braga Hospital, Braga, Portugal; Department of Clinical Epidemiology, Predictive Medicine and Public Health, Faculty of Medicine of Porto University, Porto, Portugal; francisco.botelho@gmail.com

Address of corresponding author:
Rua Afonso Baldaia, nº 775, bloco 781, apart. 341; 4150-018 Porto, Portugal; mariana_santiago_3@hotmail.com

Main manuscript

Hormone levels and Peyronie's disease: more than testosterone deficiency?

ABSTRACT

Introduction. A potential relationship between testosterone deficiency (TD) and Peyronie's disease (PD) has been repeatedly suggested. However, other hormone levels may influence the pathogenesis of PD, indicating the need for a complete hormonal assessment.
Aims. To evaluate the association of comorbidities and hormonal profile with PD, and the relationship of hormone levels with PD's severity, including penile vascular dysfunction.
Methods. We retrospectively selected 63 consecutive patients and 65 controls from our Andrology consult. Demographic, clinical, hormonal profiles and Penile Duplex Doppler Ultrassound (PDDU) measurements were collected. TD was defined as total testosterone (TT) below 350 ng/dL and PD patients with TD (Group 1) were compared with those with normal TT levels (Group 2).
Main Outcome Measures. Identification of comorbidities and hormonal profile in PD patients compared to a control group, and correlation of characteristics of PD with hormone levels and PDDU values.
Results. There were no significant differences between PD patients and the control group with respect to demographic and clinical data, except for age. Follicle-stimulating hormone levels (FSH) were significantly higher in cases than in controls (5.1mUI/ml vs. 4.2mUI/ml, respectively; *P*=0.048). Free testosterone and bioavailable testosterone were significantly lower in PD patients than in controls (8.0ng/dL vs. 9.15ng/dL, *P*=0.014, and 192.4ng/dL vs. 221.1ng/dL, *P*=0.015, respectively). Patients with PD presented more TD than controls, but with no significant difference (56.3% vs. 43.8%, *P*=0.475). Prolactin levels were directly correlated with curvature's degrees (r=0.375; *P*=0.003) and with the plaque length (r=0.391; *P*=0.002), and FSH levels were positively correlated with the plaque length (r=0.299; *P*=0.018). Plaque length was significantly higher in group 1 than in group 2 (4.1±1.6cm vs. 3.2±1.03cm; *P*=0.048), with no significant difference regarding the plaque width.
Conclusion. We demonstrated a relationship between hormone levels and PD, beyond TD, which might interfere in the pathophysiology of this disease.

Key Words. Peyronie's Disease; Testosterone; Hormone levels; Penile Curvature; Hypogonadism; Comorbidities

Introduction

Peyronie's disease (PD) is a localized fibrotic disorder involving the tunica albuginea of the penis. This acquired, benign condition results in penile deformities, mainly penile curvature, pain on erection, and, in some men, erectile dysfunction (ED). Consequently, PD is often physical and psychologically devastating for patients and may negatively impact partner relationships [1-4].

PD was thought to be an uncommon disorder. Nevertheless, contemporary studies have estimated the prevalence rate of the disease at approximately 5%, or even higher [1, 4].

Although the etiology and underlying pathophysiology of PD are not completely understood, scarring is most likely the end result of trauma, as a known or occult event, or repeated microtrauma to the erect penis in genetically susceptible men, leading to inflammation, fragmentation of elastic fibers and deposition of excessive collagen [1, 2, 5]. However, it is still unclear why the peak onset of PD occurs among men in their fifties if trauma is the precipitant event, as the frequency of sexual intercourse tends to be greater in young men. One possibility is a cumulative effect of repetitive minor injuries to the tunica albuginea over time, and a recent study suggests that it may be due to relatively low serum testosterone levels in older man [5].

Comorbid systemic diseases have been shown to increase the risk for developing more severe PD, independent of age [2]. Patients with diabetes mellitus (DM) and/or hypercholesterolemia were at a significantly higher risk of experiencing severe (> 60°) penile curvature [2, 6-9]. PD is also strongly associated with Dupuytren's contracture [1, 10, 11]. Approximately 20% of PD men will demonstrate this autosomal dominant fibrotic condition [1]. However, the impact of these comorbidities on the severity of penile curvature is still controversial and most studies do not examinate the serum testosterone levels as a risk factor for PD [8, 12]. Moreno et al. considered this last aspect, but did not included a control group in their investigation [9].

As testosterone has been shown to influence wound healing, and serum testosterone levels declines in the age group at risk for PD, Moreno et al. measured the prevalence of testosterone deficiency (TD) in PD patients and correlated serum concentrations of testosterone with the severity of penile curvature. This study identified a strong association between PD and low testosterone serum concentrations, as 74.4% of men with PD demonstrated low levels of testosterone and PD patients with low testosterone levels had a significantly greater degree of penile curvature than men with normal testosterone serum concentrations (54.3° vs. 37.1°, respectively, P=0.006) [2, 9]. Furthermore, a recent study suggested that the presence of TD was associated with a significantly greater mean degree of penile curvature and a larger plaque size, with no difference regarding pain on erection's complain [5].

Other study found that bioavailable testosterone (bT) and free testosterone (fT) were significantly lower and luteinizing hormone (LH) and sex hormone-binding globulin (SHBG) were significantly higher in PD group than in control patients [13]. The plaque area was significantly larger in PD group with low bT/fT than in patients with normal bT/fT, not only confirming the findings of Moreno et al. [9], but also including a control group [13]. Moreover, this was

the first study that assessed the androgenic levels of the populations studied, indicating the need for a complete hormonal assessment in PD patients and suggesting that further investigation is necessary to confirm the potential relationship between low testosterone levels and PD [13].

Aims

In the present study, we aim to comprehensively evaluate the association of systemic comorbidities and hormonal profile with PD, and the relationship of hormone levels with the severity of this disease, including penile vascular dysfunction.

Methods

We retrospectively selected 63 consecutive patients with PD and 65 controls followed in the Andrology consult of S. João Hospital from July 2007 until December 2013.

The diagnosis of PD was made on the basis of the presence of characteristic symptoms and a palpable plaque on routine examination of the penis, or an acquired penile curvature confirmed and characterized by an intracavernosal injection of 10 mcg of commercial E1 prostaglandin at the time of performing Penile Duplex Doppler Ultrasound (PDDU).

Clinical, traumatic and sexual history was gathered for patients with PD, including age at diagnosis, pain on erection, duration of symptoms, penile trauma history, type and degrees of penile curvature, and comorbidities. DM, hypertension, hypertriglyceridemia and hypercholesterolemia were defined as the report of a physician's diagnosis of the condition or according with the use of medication to control the comorbidity. Smoking was evaluated by questions about current, past or never existed habits. The severity of penile curvature was classified using the Kelami system in: grade 1 – curvature 30° or less, grade 2 – 30° to 60°, and grade 3 – greater than 60° [5, 12]. Length and width of the penile plaque were determinated by physical examination.

PDDU measurements were carried out by a single physician, using the protocol suggested by the International Society for Sexual Medicine Standards Committee in Standard Practice in Sexual Medicine. A 12MHz transducer (GE Logic 7 Ultrasound System, UK) was used to record penile vascular flow patterns 5, 10 and 20 minutes after the injection of 10 to 20 mcg of commercial E1 Prostaglandin (Caverject®). Before and in-between evaluations, patients were left alone to prevent disturbances and consequent loss of sexual arousal, and asked to maintain the best possible erection by tactile stimulation. The mean values of Peak Systolic Velocity (mPSV), End-Diastolic Velocity (mEDV) and Resistive Index (RI) were obtained from spectral waveform measurements. The classification criteria were the following: absence of ED for mPSV**>**35 cm/s, EDV**<**5 cm/s and RI**>**1; arterial dysfunction for mPSV**≤**35 cm/s; mPSV asymmetry dysfunction for an asymmetry in mPSV**>**10 cm/s; cavernous venous-occlusive dysfunction for mPSV**≥**35 cm/s and EDV**≥**5 cm/s; and mixed dysfunction when 35**>**PSV**>**25 cm/s and EDV**≥**5 cm/s [14, 15].

As a control group, we selected men who were referred to our Andrology unit and did not reveal evidence of PD. Men with a history of ED and/or receiving

hormonal treatment or other treatment that might influence the variables to be measured were also excluded. All of them gave their informed consent for participating in the study and had a complete hormonal assessment available.

Total testosterone (TT), SHBG, estradiol, prolactin (PRL), follicle-stimulating hormone (FSH) and LH were determined by chemiluminescence with a commercially available kit (Cobas; Roche Diagnosis GmbH, Manheim, Germany). Levels of fT and bT were calculated using the *Free and Bioavailable Testosterone calculator*, developed at the Hormonology Department, University Hospital of Ghent, Belgium (http://www.issam.ch/freetesto.htm). The ratio estradiol/TT was also calculated and albumin was measured by routine laboratory methods. The electronic process of each patient and available digitalized records were also consulted.

In the present study, TD was defined as TT below 350 ng/dL [5]. Patients with PD and TD (Group 1) and those with normal TT levels (Group 2) were compared according to age, systemic comorbidities, TT serum concentration, PD's mean duration, penile trauma history, pain on erection, length and width of the plaque, type and severity of curvature, curvature degrees and PDDU values.

Groups were compared with Chi-Squared test, Kruskall-Wallis test or Student's *t*-test as appropriate, and Spearman correlation coefficients were computed to quantify the association between continuous variables. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS®, 18.0 version). A *P* value of < 0.05 was considered statistical significant. Sample size was computed using S*Power 3.1.4 software considering a α of 0.05, a β of 0.20, an effect size of 0.5, and a ratio case/control of 1. For a two-tailed analysis, the required sample size was 64 individuals in each group with a total sample size of 128.

Main Outcome Measures

Identification of comorbidities and hormonal profile in PD patients compared to a control group, and correlation of characteristics of PD with hormone levels and PDDU values.

Results

The demographic, clinical and hormonal profiles of PD patients and control population are shown in Table 1. The mean age was significantly different in both groups, being 57.4 ± 6.8 years in cases and 51.8 ± 10.2 years in controls (*P*<0.001).

The most commonly PD's associated comorbidity was hypertension. This condition was more prevalent in PD patients than in the control group, but did not reach statistical significance (53.4% vs. 37.5%, *P*=0.113).

The FSH levels were significantly higher in cases than in the control group (5.1 mUI/ml vs. 4.2 mUI/ml, respectively; *P*=0.048). Serum concentrations of fT and bT were significantly lower in the PD group than in controls (8.0 ng/dL vs. 9.15 ng/dL, *P*=0.014, and 192.4 ng/dL vs. 221.1 ng/dL, *P*=0.015, respectively). Although TT serum concentration was also lower in cases than in controls, it did not reach statistical significance (457.4 ng/dL vs. 484.6

ng/dL, respectively; *P*=0.392). Moreover, the estradiol/TT ratio and the mPSV were also lower in the PD population than in the control group, but with no significant difference.

The median of duration of symptoms was approximately 12 months. Penile trauma was reported by 6.7% of the patients, and 58.1% reported pain on erection. Penile curvature degrees' median was 45°, with 44.3% of PD patients having curvature > 60° (grade 3), 39.3% between 30 and 60° and 16.4% < 30°. The direction of primary curvature was dorsal in 63.5%, ventral in 4.8%, lateral in 25.4 % and with hourglass deformity in 6.3% of PD patients. The medians of plaque length and width were 3.0 and 2.0 cm, respectively. In PD group, 69.8% did not have ED. However, 12.7% had arterial dysfunction and 17.5% venous-occlusive dysfunction. Dupuytren's contracture was present in 29% of PD patients.

Furthermore, the percentage of TD was higher in PD patients than in controls, but again with no significant difference (56.3% vs. 43.8%, *P*=0.475).

Correlating characteristics of PD with the hormone profile and the PDDU measurements, we found that PRL levels were directly correlated with the degrees of curvature (r=0.375; *P*=0.003) and with the plaque length (r=0.391; *P*=0.002), and FSH levels were positively correlated with the plaque length (r=0.299; *P*=0.018). In addition, SHBG levels were positively correlated with the ratio estradiol/TT levels (r=0.396; *P*<0.01).

The degrees of penile curvature were directly correlated with the duration of symptoms (r=0.275; *P*=0.033). However, TT, bT and fT levels were not directly correlated with the duration of symptoms, curvature degrees and length/width of the plaque.

Moreover, there were no significant statistical associations between the severity of curvature with PD patients' age, their hormone profile and PDDU values.

Comparison of PD population with TD vs. normal TT levels is presented in Table 2. The mean duration of PD was similar in patients in groups 1 and 2 (10.6 vs. 12.4 months, respectively). Plaque length was significantly higher in group 1 than in group 2 (4.1 ± 1.6 cm vs. 3.2 ± 1.03 cm; *P*=0.048), whereas there was no significant difference in width plaque. The mean of penile curvature degrees was slightly greater in group 1 compared with group 2, but did not reach statistical significance (57.9% vs. 54.8%, *P*=0.583). The frequency of severe penile curvature was also greater in group 1 than in group 2 (52.9% vs. 40.9%, *P*=0.602). Moreover, PDDU measurements did not differ between groups 1 and 2.

Discussion

The results of this retrospective study revealed no statistical significant relationship between common comorbidities and PD, apparently refuting the majority of contemporary evidence about this issue [1, 2, 16]. Nevertheless, our data are in line with the trend suggested by Rhoden et al., as we also found a non-significative trend towards higher prevalence of hypertension in PD patients [11]. We also corroborate the findings of Usta et al. that, although systemic comorbidities were commonly seen in PD patients, there were no statistical relationship between penile curvature severity and any of these comorbidities or PDDU values [12].

In our study, the percentage of TD was higher in PD patients than in controls, but with no significant difference, contrary to others that observed a significantly higher incidence of TD in PD patients than in the age-matched controls (76.5% vs. 41.2%, *P*<0.0001), suggesting a pathophysiologic role for TD in PD [17]. Two theories were proposed for low testosterone to be related with PD: (1) reduced erectile rigidity, by the important association of testosterone with erection and (2) impaired tissue response to injury with low testosterone levels [5, 9]. Adequate testosterone levels are required for insulin-like growth factor (IGF)-1 production and IGF-1 is a wound healing agent [5, 18]. Moreover, transforming growth factor (TGF)-β1 is overexpressed in PD. TGF-β1 stimulates collagen synthesis and induces other profibrotic factors' production [5, 9, 19]. Evidence demonstrated that testosterone was involved in the downregulation of TGF-β1 production [5]. Therefore, testosterone is a necessary androgen to maintain the wound healing response. A TD results in catabolism and impaired healing [5, 18]. Reduced rigidity might lead to greater penile bending, thus predisposing the penis to microtrauma and PD [5, 20].

The main impetus of the present study was to determinate if the hormone profile was associated with PD and with the severity of PD. These potential relationships received only minor investigation to date, with only one study reporting results about both outcomes [13]. Our study corroborated their findings in terms of fT and bT levels, which were significantly lower in the PD patients' group than in controls, and plaque length, that was significantly higher in PD patients with TD. However, we did not find significant correlation of TD with symptoms' duration and curvature degrees.

Serum concentrations of fT and bT are generally considered more reflective of androgen status than TT values, as they are not confounded by SHBG levels. Therefore, studies using these two parameters might be more relevant to evaluate if low testosterone plays a potential role in the development of PD [9, 13].

A significant correlation between the ratio estradiol/TT with the severity of penile curvature (r=0.476, P=0.0001) was observed by Moreno et al., although no explanation was suggested for how or why estradiol may contribute to PD [9]. As the aging process continues uncontested and testosterone levels decrease with age, there is a relative accumulation of fatty tissue and aromatization accelerates the conversion of testosterone to estradiol. This additional secondary estradiol inhibition results in the maintenance of a TD state [21, 22]. Despite of the fact that we did not find a statistical significant correlation, further investigation about this item may be an important step for improving our understanding of PD.

This was the first study reporting positive correlations between other hormone levels than testosterone with the severity of the PD. Serum concentrations of PRL were directly correlated with the degrees of curvature and with the plaque length, as well as FSH levels were positively correlated with the plaque length. It remains unknown how and why PRL and FSH levels contribute to PD. Evidence suggests that TD is associated with the severity of PD and that severe hyperprolactinemia inhibits testosterone secretion [9, 23]. However, despite of PRL levels being higher in PD patients than in controls, they were in the normal range. Nevertheless, a TD continuous state can

explain not only the stimulation of FSH production, but also its influence on the severity of the disease.

Moreover, we were the first to investigate if TD was associated with PDDU measurements in PD patients. These values were similar in groups 1 and 2, but as evidence reports a strong association between TD and ED in aging men [24] and ED is present in a high percentage of men with PD, varying from 20 to 54% [11, 25], this association may deserve further studies.

There were some limitations in our study, one being its retrospective design. Because of small sample size, the statistical power of the analysis was limited. A 31-year age spread in a relatively small sample size of PD patients might have interfered with data analysis. Thus, studies using larger samples are still required to elucidate the true association between hormone levels and PD characteristics.

Conclusion

Our investigation suggested a possible relationship between hormone levels and PD, beyond TD. Furthermore, low levels of fT and bT were the biggest contribution to TD in PD patients. Although these parameters were not correlated with severity of PD, they were significantly lower in PD patients, corroborating the potential role of low testosterone in the pathophysiology of this disease.

Therefore, further studies, namely prospective trials with a complete hormonal assessment in PD patients, are needed to confirm or refute this evidence.

Conflict of Interest: None declared.

References

1. Bella AJ, Perelman MA, Brant WO, Lue TF. Peyronie's disease (CME). J Sex Med. 2007;4(6):1527-38.
2. Garaffa G, Trost LW, Serefoglu EC, Ralph D, Hellstrom WJ. Understanding the course of Peyronie's disease. Int J Clin Pract. 2013;67(8):781-8.
3. El-Sakka AI, Salabas E, Dinçer M, Kadioglu A. The pathophysiology of Peyronie's disease. Arab Journal of Urology. 2013;11(3):272-7.
4. Karavitakis M, Komninos C, Simaioforidis V, Kontos S, Lefakis G, Politis V, et al. The relationship between androgens, regulators of collagen metabolism, and Peyronie's disease: a case control study. J Sex Med. 2010;7(12):4011-7.
5. Nam HJ, Park HJ, Park NC. Does testosterone deficiency exaggerate the clinical symptoms of Peyronie's disease? Int J Urol. 2011;18(11):796-800.
6. Kendirci M, Trost L, Sikka SC, Hellstrom WJ. Diabetes mellitus is associated with severe Peyronie's disease. BJU Int. 2007;99(2):383-6.
7. Grasso M, Lania C, Blanco S, Limonta G. The natural history of Peyronie's disease. Arch Esp Urol. 2007;60(3):326-31.
8. Kadioglu A, Tefekli A, Erol B, Oktar T, Tunc M, Tellaloglu S. A retrospective review of 307 men with Peyronie's disease. J Urol. 2002;168(3):1075-9.
9. Moreno SA, Morgentaler A. Testosterone deficiency and Peyronie's disease: pilot data suggesting a significant relationship. J Sex Med. 2009;6(6):1729-35.
10. Qian A, Meals RA, Rajfer J, Gonzalez-Cadavid NF. Comparison of gene expression profiles between Peyronie's disease and Dupuytren's contracture. Urology. 2004;64(2):399-404.
11. Rhoden EL, Riedner CE, Fuchs SC, Ribeiro EP, Halmenschlager G. A cross-sectional study for the analysis of clinical, sexual and laboratory conditions associated to Peyronie's disease. J Sex Med. 2010;7(4 Pt 1):1529-37.
12. Usta MF, Bivalacqua TJ, Jabren GW, Myers L, Sanabria J, Sikka SC, et al. Relationship between the severity of penile curvature and the presence of comorbidities in men with Peyronie's disease. J Urol. 2004;171(2 Pt 1):775-9.
13. Cavallini G, Biagiotti G, Lo Giudice C. Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. J Androl. 2012;33(3):381-8.
14. Tomada N, Tomada I, Botelho F, Cruz F, Vendeira P. Are all metabolic syndrome components responsible for penile hemodynamics impairment in patients with erectile dysfunction? The role of body fat mass assessment. J Sex Med. 2011;8(3):831-9.
15. Porst H, Buvat J. Standard practice in sexual medicine Oxford: Blackwell Publishers; 2006. 149–57 p.
16. Bjekic MD, Vlajinac HD, Sipetic SB, Marinkovic JM. Risk factors for Peyronie's disease: a case-control study. BJU Int. 2006;97(3):570-4.
17. Sturm R, Rumohr JA, Lipshultz LI, Mohamed O, Khera M. Increased incidence of hypogonadism in patients with a novel diagnosis of peyronie's

disease as compared to organic erectile dysfunction. J Urol. 2009;181(4):278-9.
18. Demling RH. The role of anabolic hormones for wound healing in catabolic states. J Burns Wounds. 2005;4:e2.
19. Gonzalez-Cadavid NF, Magee TR, Ferrini M, Qian A, Vernet D, Rajfer J. Gene expression in Peyronie's disease. Int J Impot Res. 2002;14(5):361-74.
20. Rhoden EL, Buselato LG, Ting HY, Teloken C, Souto CA. Is there any association between Peyronie's disease and serum collagen markers? Int J Impot Res. 2000;12(6):302-4.
21. Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. J Androl. 2009;30(1):10-22.
22. Cohen PG. The role of estradiol in the maintenance of secondary hypogonadism in males in erectile dysfunction. Med Hypotheses. 1998;50(4):331-3.
23. Maggi M, Buvat J, Corona G, Guay A, Torres LO. Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). J Sex Med. 2013;10(3):661-77.
24. Iacono F, Prezioso D, Ruffo A, Illiano E, Romis L, Di Lauro G, et al. Testosterone deficiency causes penile fibrosis and organic erectile dysfunction in aging men. Evaluating association among Age, TDS and ED. BMC Surg. 2012;12 Suppl 1:S24.
25. Chung E, De Young L, Brock GB. Penile duplex ultrasonography in men with Peyronie's disease: is it veno-occlusive dysfunction or poor cavernosal arterial inflow that contributes to erectile dysfunction? J Sex Med. 2011;8(12):3446-51.

Tables

Table 1 Demographic, clinical and hormonal profiles of PD patients and control population

	PD patients	Controls	*P* value*
Number of subjects	63	65	
Age (years)	57.4 ± 6.8	51.8 ± 10.2	< 0.001
Hypertension	31 (53.4%)	24 (37.5%)	0.113
Diabetes mellitus	19 (35.2%)	24 (37.5%)	0.946
Hypercholesterolemia	20 (36.4%)	32 (54.2%)	0.084
Hypertriglyceridemia	13 (24.5%)	20 (33.9%)	0.380
Smoking			< 0.001
- Never smoking	51 (82.3%)	25 (39.1%)	
- Current smoking	9 (14.5%)	17 (26.6%)	
- Past smoking	2 (3.2%)	22 (34.4%)	
Sex hormone-binding globulin (nmol/L)	36.8 (30.1-52.7)	35.8 (26.8-49.8)	0.312
Albumin (g/L)	44.1 ± 2.5	44.3 ± 2.9	0.600
Follicle-stimulating hormone (mIU/mL)	5.1 (4.0-7.8)	4.2 (3.3-6.2)	0.048
Luteinizing hormone (mIU/mL)	4.3 (3.3-5.9)	4.2 (2.9-5.6)	0.340
Total testosterone (ng/dL)	457.4 ± 172.6	484.6 ± 185.3	0.392
Free testosterone (ng/dL)	8.0 ± 2.3	9.15 ± 2.7	0.014
Bioavailable testosterone (ng/dL)	192.4 ± 56.8	221.1 ± 69.9	0.015
Prolactin (ng/ml)	7.9 ± 6.8	7.6 ± 3.4	0.800
Estradiol (pg/ml)	27.5 ± 13.3	32.2 ± 18.2	0.110
Estradiol (pg/ml)/total testosterone (ng/dL)	0.063 ± 0.032	0.077 ± 0.058	0.110
mPSV (cm/s)	49.3 ± 19.6	53.5 ± 14.5	0.235
mEDV (cm/s)	0.0 (0.0-5.1)	0.0 (0.0-3.8)	0.168
RI	1.0 (0.9-1)	1.0 (1.0-1.0)	0.054

Data are presented as the mean ± standard deviation, median (percentile 25-percentile 75) or number of subjects in each group with percentages in parentheses, as appropriate. PD = Peyronie's disease; mPSV = mean values of Peak Systolic Velocity; mEDV = mean values of End-Diastolic Velocity; RI = Resistive Index. *Significance level at $P < 0.05$.

Table 2 Distribution of Peyronie's disease (PD) according to total testosterone (TT) levels

	Group 1	Group 2	*P* value*
Number of subjects	18	45	0.475
Age (years)	56.1 ± 6.9	57.9 ± 6.8	0.345
Smoking (%)			0.262
- Never smoking	94.4	77.3	
- Current smoking	5.6	18.2	
- Past smoking	0.0	4.5	
Hypercholesterolemia (%)	43.8	33.3	0.674
Hypertriglyceridemia (%)	26.7	23.7	0.822
Hypertension (%)	37.5	59.5	0.227
Diabetes mellitus (%)	43.8	31.6	0.587
Dupuytren's contracture (%)	11.1	36.4	0.093
Total testosterone (ng/dL)	300.1 ± 46.5	520.3 ± 164.2	<0.001
Duration of PD (months)	10.6 ± 4.8	12.4 ± 10.4	0.481
History of penile trauma (%)	12.5	4.5	0.287
Pain on erection (%)	58.8	57.8	0.941
Plaque length (cm)	4.1 ± 1.6	3.2 ± 1.03	0.048
Plaque width (cm)	1.8 ± 0.6	1.9 ± 0.7	0.431
Curvature type (%)			0.987
- dorsal	61.1	64.4	
- ventral	5.6	4.4	
- lateral	27.8	24.4	
- hourglass deformity	5.6	6.7	
Curvature degrees	57.9 ± 20.2	54.8 ± 20.1	0.583
Curvature severity (%)			0.602
- < 30° (grade 1)	17.6	15.9	
- 30-60° (grade 2)	29.4	43.2	
- > 60° (grade 3)	52.9	40.9	
Erectile dysfunction diagnosis (%)			0.394
- absence of erectile dysfunction	61.1	73.3	
- arterial dysfunction	11.1	13.3	
- venous-occlusive dysfunction	27.8	13.3	

mPSV (cm/s)	50.00 ± 24.2	48.99 ± 17.6	0.870
mEDV (cm/s)	3.56 ± 5.3	3.22 ± 4.3	0.813
RI	0.93	0.95	0.451

Data are presented as the mean ± standard deviation or percentage, as appropriate, for a total of 18 PD patients with TD (Group 1) and 45 patients with normal TT levels (Group 2). mPSV = mean values of Peak Systolic Velocity; mEDV = mean values of End-Diastolic Velocity; RI = Resistive Index.*Significance level at $P < 0.05$.

Agradecimentos

Ao Prof. Doutor Nuno Tomada, meu orientador, pela disponibilidade e revisão da presente dissertação.

Ao Dr. Francisco Botelho, pelo apoio e análise estatística.

Ao Serviço de Urologia do Hospital de São João, por me permitir elaborar este trabalho.

Anexos

Guidelines da revista *The Journal of Sexual Medicine*

SUBMISSION
The Journal of Sexual Medicine requires that authors submit electronically via the ScholarOne Manuscripts online submission site at http://mc.manuscriptcentral.com/jsm. Complete, detailed instructions on uploading your manuscript are detailed below.

First click on the "Check for Existing Account" button on the opening page of the website (the bottom of the two buttons). If you do not already have an account, then create an account for yourself by clicking on the "Create an Account" button. You will then be able to submit and monitor the progress of your manuscripts. Follow the submittal instructions carefully.

At the end of a successful submission, a confirmation screen with manuscript number will appear and you will receive an E-mail confirming that the manuscript has been received by the journal. If this does not happen, please check your submission and/or contact the editorial office at jsm@issm.info. Through individual Author Centers on this website, authors can view the status of their

manuscripts as they progress through the review process.

Any major word processor software may be used, and both DOS-based and Macintosh operating systems are acceptable.

REFERRALS TO SEXUAL MEDICINE

The Journal of Sexual Medicine works together with the ISSM's new Open Access Journal, *Sexual Medicine*, to enable rapid publication of good quality research that we are unable to accept for publication in our journal. Authors, whose papers are rejected by *The Journal of Sexual Medicine*, may be offered the option of having the paper, along with any related peer reviews, automatically transferred for consideration by the Editors of *Sexual Medicine*. Publication decisions will be made a short time after the transfer takes place. The Editors of *Sexual Medicine* will accept submissions that report well-conducted research which reaches the standard acceptable for publication. *Sexual Medicine* is an Open Access journal and article publication fees apply. For more information please go to www.sm.issm.info.

Please note that if you are an author or reviewer for *The Journal of Sexual Medicine*, you automatically have an account with *Sexual Medicine* and you should use the same login information for submission to that journal that you use for the other journal.

AIMS AND SCOPE

The Journal of Sexual Medicine publishes multidisciplinary basic science and clinical research to define and understand the scientific basis of male, female, and couple's sexual function and dysfunction. As an official journal of the International Society for Sexual Medicine and the International Society for the Study of Women's Sexual Health, it provides healthcare professionals in sexual medicine with essential educational content and promotes the exchange of scientific information generated from experimental and clinical research.

The Journal of Sexual Medicine includes basic science and clinical research studies in the psychologic and biologic aspects of male, female, and couple's sexual function and dysfunction, and highlights new observations and research, results with innovative treatments and all other topics relevant to clinical sexual medicine.

The objective of *The Journal of Sexual Medicine* is to serve as an interdisciplinary forum to integrate the exchange among disciplines concerned with the whole field of human sexuality. The journal accomplishes this objective by publishing original articles, as well as other scientific and educational documents that support the mission of the International Society for Sexual Medicine.

International Society for Sexual Medicine Mission

Specifically, the ISSM aims:

• To establish a scientific Society to benefit the public by encouraging the highest standards of practice, education and research in the field of human sexuality;

• To develop and assist in developing scientific methods for the diagnosis, prevention and treatment of conditions affecting human sexual function;
• To promote the publication and encourage contributions to the medical and scientific literature in the field of sexual function.

MANUSCRIPT TYPES
The Journal of Sexual Medicine publishes several types of manuscripts. A brief description of each type follows:

- Original Research
- Reports and Brief Reports
- Reviews
- Editorials
- Continuing Medical Education
- Calendar

Original Research
Original research papers are scientific reports from original research in sexual medicine. As a general guideline, manuscripts should be 3,000 words in length; more extensive manuscripts will be considered and judged on merit; however, authors are urged to be as concise as possible. All manuscripts must include an abstract, a maximum of 7 tables and figures (total), and up to 50 references. More may be accepted if justified.

Reports
Reports usually describe one to three patients with pertinent conditions. Brief Reports are concise reports of cases, clinical experience, clinical studies, drug trials, adverse effects, or devices related to sexual medicine. Maximum length of text is 1,750 words; no more than 10 bibliographic references and one figure or table per case.

Reviews
Review articles are timely, in-depth treatment of an issue. Reviews are usually solicited by the editors, but unsolicited materials will be considered. The text should be approximately 5,000 words, with an abstract, a maximum of 7 tables and figures (total), and up to 75 references. More references may be accepted if justified. Review articles undergo the same peer-review and editorial process as all other manuscripts submitted to the journal.

Editorials

Editorials provide opinions of recognized leads in the field. Editorials providing commentary and analysis of an article in a particular issue of the journal are always solicited. Authors of the original paper will be given opportunity to respond to the editorial comment in the same issue. Editorial comments are limited to 1,000 words, with up to 7 references.

Letters to the Editor

Letters to the Editor, subject to editing, are considered for publication provided they do not contain material submitted or published elsewhere. The text must not exceed 500 words or have more than five references and one figure or table. Letters referring to a published article must be received within four months of the article's publication. Continuing Medical Education Continuing Medical Education articles are always solicited. Calendar This is a section in the back of the journal for news and meeting announcements from ISSM and its Regional Affiliate Societies, as well as other appropriate meeting announcements. Please send contributions to this section directly to jsm@issm.info.

GENERAL INSTRUCTIONS

Manuscripts must be submitted in grammatically correct English, with spelling and phrasing consistent throughout the paper. Manuscripts that do not meet this standard cannot be reviewed.

English-Language Editing Services

Authors for whom English is a second language may wish to consult an English-speaking colleague or consider having their manuscript professionally edited before submission to improve the English. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

Simultaneous Submission

A manuscript is considered for review and possible publication on the condition that it is submitted solely to *The Journal of Sexual Medicine*, and that the manuscript or a substantial portion of it is not under consideration elsewhere. In order for a manuscript to be considered for publication all named authors must agree 1) to its submission, 2) that it is not currently being considered for publication by another journal, and 3) if accepted, the paper will not subsequently be published in the same or similar form in any language without the written consent of the publisher.

Manuscript Structure

Each manuscript must contain the following structured headings:

- Abstract
- Introduction
- Aims
- Methods
- Main Outcome Measures
- Results
- Discussion
- Conclusions
- References

Reporting Checklists

It is strongly recommended, where appropriate, that you ensure your manuscript conforms to a reporting guideline that best fits your type of manuscript. For example, a CONSORT statement should be completed and uploaded with your manuscript for a Randomized Controlled Trial. The International Society for Sexual Medicine (ISSM) Publication Reporting Guidelines detail the appropriate checklist(s) to use per study type.

We urge you when completing your reporting checklist to take the time to ensure your manuscript meets these basic reporting needs. In doing so, you will greatly enhance your chances of publication.

Randomized Controlled Trials

Reports of Randomized Controlled Trials (RCTs) must state explicitly how the comparison groups were generated, so that readers will be able to assess the method of randomization. In the title and abstract, specify that the manuscript is a report of an RCT. Prior to submitting an RCT manuscript; authors should refer to the CONSORT checklist (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285:1987–1991).

Clinical Trial Registry

The Journal of Sexual Medicine requires that all prospective, randomized, controlled trials with patient enrollment starting on or after August 1, 2007, be registered in a public database that meets the requirements of the World Health Organization. Currently, such registries include the following: www.actr.org.au, www.clinicaltrials.gov, www.ISRCTN.org, www.umin.ac.jp/ctr/index/htm, and www.trialregister.nl.

For more information, please refer to the guidelines at http://www.icmje.org/#clin_trials. Upon submission, please provide the

registration identification number and the URL for the trial's registry in your cover letter.

Reports of Diagnostic Tests
Authors of reports of diagnostic tests are encouraged to submit the STARD flow diagram and checklist (Bossuyt PM, Reitsma JB, Bruns DF, et al. for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Clin Chem. 2003;49:1-18).

Cell Line Authentication
To ensure the highest standards of quality and accuracy, *The Journal of Sexual Medicine* strongly encourages the authentication of cell lines used in the research submitted to the journal. Manuscripts based on research using cell lines must include a statement addressing the following points in the Methods section of the manuscript:
1. Where the cells were obtained from
2. Whether the cell lines have been tested and authenticated
3. The method by which the cells were tested
If cells were obtained directly from a cell bank that performs cell line characterizations and passaged in the user's laboratory for fewer than 6 months after receipt or resuscitation, re-authorization is not required. In these cases, please include the method of characterization used by the cell bank. If the cell lines were obtained from an alternate source, authors must provide authentication of the origin and identity of the cells. This is best achieved by DNA (STR) profiling. The DNA profile should be cross-checked with the DNA profile of the donor tissue (in case of a new cell line) or with the DNA profile of other continuous cell lines.

Gene names and genetic profiling data: Please mark all gene names in italics. However, only the gene names should be written in italics, to distinguish them from gene products, gene segments, clusters, families, complexes, or groups. Authors should only use the official gene name as assigned by the respective gene nomenclature committee. Regarding comprehensive data sets of genetic profiling (microarray) studies, raw data must be in a publicly available database that requires MIAME format (for example, "GEO" or "Array Express") upon submission of a paper. Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL and GenBank on a daily basis. The suggested wording for referring to accession-number information is: 'These sequence data have been submitted to the DDBJ/EMBL/GenBank databases under accession number U12345.'

Statistical Guidelines
All submitted manuscripts containing data analyses will be evaluated for the integrity of the statistical methods as well as a sufficient description of the methodological approach. This will entail evaluation of the study design,

statistical analysis and presentation and interpretation of study results. As a general guideline, readers of the manuscript should be able to replicate the analysis with the same data based on the description given in the Methods section. Authors are encouraged to carefully select language in the Discussion that is appropriate given the study design and refrain from causal inferences from observational (nonrandomized) studies.

Authors should also be explicit about the limitations of the study. Failure to disclose important limitations upon submission will be viewed with greater scrutiny than those clearly discussed. Key elements which should be consistent for all submitted manuscripts include the following:

- Report the sample size n for each study and each analysis
- Describe the power analysis to justify the sample size if appropriate
- Identify all statistical methods and verify the assumptions for all statistical tests
- Provide alpha (the probability of a Type I error) for all statistical tests
- Specify whether tests are one- or two-sided
- Report the descriptive statistics (n, mean, median, and standard deviation) for all continuous variables
- Report n and the sample proportion for binary variables
- Adequately explain complex statistical procedures such a multivariate logistic regression and the Cox proportional hazards regression model and verify the assumptions of each such procedure
- Report the actual P-values and explain what is meant by statistical significance
- Discuss and describe adjustments for multiple testing

Ethics

All manuscripts must conform to the policies outlined in the ISSM Publication Guidelines.

Informed Consent

The Journal of Sexual Medicine requires that all appropriate steps be taken in obtaining informed consent of any and all human and/or experimental animal subjects participating in the research comprising the manuscript submitted for review and possible publication. A statement indicating that the protocol and procedures employed were reviewed and approved by the appropriate institutional review committee must be included in the Methods section of the manuscript. For research involving recombinant DNA, containment facilities and

guidelines should conform to those of the National Institutes of Health or corresponding institutions. For those investigators who do not have formal ethics review committees, the principles outlined in the Helsinki Declaration of 1975, as revised in 1983, should be followed. A statement is required with any report of investigations involving human subjects confirming that informed consent was obtained from the subject(s) and/or guardian(s). It should be stated clearly in the manuscript that informed consent was obtained.

Photographs with Identifiable Patients

In photographs, sonograms, CT scans, etc., the physical identification of a patient should be masked whenever possible. If a patient is identifiable, written permission to use the photograph must be obtained from the patient or guardian and sent to *The Journal of Sexual Medicine* Editorial Office upon manuscript submission. Clearly state in the manuscript that informed consent has been obtained.

Disclosure Statement

The Journal of Sexual Medicine requires that all authors disclose any potential sources of conflict of interest. Any interest or relationship, financial or otherwise, which might be perceived as influencing an author's objectivity, is considered a potential source of conflict of interest. These must be disclosed when directly relevant or directly related to the work that the authors describe in their manuscript. Potential sources of conflict of interest include, but are not limited to, patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a conflict of interest does not preclude publication in any ISSM journals. If the authors have no conflict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to list on the cover letter to the Editor-in-Chief, in the manuscript (under the Acknowledgements section), and in the online submission system ALL pertinent commercial and other relationships.

Authors' Professional and Ethical Responsibilities

Should possible scientific misconduct or dishonesty in research submitted for review be suspected or alleged, *The Journal of Sexual Medicine* reserves the right to forward any submitted manuscript to the sponsoring or funding institution or to other appropriate authorities for investigation. The journal also screens manuscripts for incidents of plagiarism; please ensure that manuscripts present original data written in unique language.

Authorship

The Journal of Sexual Medicine requires that all authors complete an authorship statement. All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content. Authorship credit should be based only on substantial contributions to Category 1: a) conception and design, b) analysis of

data, and c) interpretation of data; and Category 2: a) drafting the article, or b) revising it critically for important intellectual content; and on Category 3) final approval of the version to be published. Categories 1, 2, and 3 must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

Editors may ask authors to describe what each contributed; this information may be published. Increasingly, multicenter trials are attributed to a corporate author. All members of the group who are named as authors, either in the authorship position below the title or in a footnote, should fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, in the Acknowledgments or in an appendix. The order of authorship should be a joint decision of the coauthors. Because the order is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to explain the order of authorship in a footnote. In deciding on the order, authors should be aware that many journals limit the number of authors listed in the table of contents and that the U.S. National Library of Medicine (NLM) lists in MEDLINE only the first 24 plus the last author when there are more than 25 authors.

Drugs and Devices

Use of generic drug names (or generic name followed by trade name in parentheses) may be used. Include manufacturer and their location (city and country) for drugs and devices.

Permissions

Information reproduced from another source must be properly cited. The corresponding author is responsible for obtaining written permission from the appropriate authors and/or copyright holders to use previously published or copyrighted material. Signed permission statements from the copyright holder for both print and online reproduction must be sent to *The Journal of Sexual Medicine* Editorial Office upon manuscript submission. Permission statements also must be obtained from at least one author when citing unpublished data, in press articles, and/or personal communications.

MANUSCRIPT PREPARATION AND SUBMISSION

In general, manuscripts should be prepared in accordance with “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” developed by the International Committee of Medical Journal Editors (www.icmje.org).

We place few restrictions on the way in which you prepare your article, and it is not necessary to try to replicate the layout of the journal in your submission. We ask only that you consider your reviewers by supplying your manuscript in a clear, generic and readable layout, and ensure that all relevant sections are included. Our production process will take care of all aspects of formatting and style.

Please use the Manuscript Submission Checklist at the end of the Author Guidelines to ensure that the manuscript has all the information necessary for successful publication.

Abstracts

Abstracts must be submitted in the appropriate field without the manuscript title or factors identifying the authors or institutions. Abstracts have a 300 word limit. Abstracts must be structured to include introduction, aim, methods, main outcome measures, results and conclusions.

Keywords

Below the abstract authors should provide, and identify as such, 4 to 10 key words or short phrases that will assist indexers in cross-indexing the article and may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of Index Medicus should be used; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

References

References are to be cited consecutively in the text typed after the final punctuation. References at the end of each manuscript should be listed in the order in which they are first cited in the text, typed double-spaced. The references should conform to the Index Medicus style, omitting number and day of month of issue. Punctuation is shown in the examples below. References to articles in press must state name of journal and if possible, volume and year.

For journal articles: all authors should be listed, title of article; name of journal; year; volume number; first and last page.
For books: surname and initials of all authors, title and subtitle, edition (other than first), publishing house, city, year, page as specific reference.
For chapters in books: surname and initials of all authors of chapter, title of chapter, editors, authors, or compilers of book, title of book, edition (other than first), publishing house, city, year, page.

1. Jones, TH, Smith, ML, Land SW. Diagnosis and treatment of erectile dysfunction. J Urol 1986;135:922-927.
2. King, RE. Sexual dysfunction in men and women. Taylor and Francis: Philadelphia 1974, 86pp.
3. Stevens RA, Otis PN. Persistent sexual arousal syndrome. In: Johnson DA, ed. Female sexual dysfunction.. Little Brown and Company: Boston, 1976, pp 100-106.

Abbreviations, Symbols, and Nomenclature

A list of acceptable abbreviations is published in the Uniform Requirements for Manuscripts submitted to Biomedical Journals (also known as the Declaration of Vancouver). For more information, refer to: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Ann Intern Med 1997;126:36-47. You may contact the Editor or

publisher directly with questions.

Quantitative data must be reported in the International System of Units (SI units).

Tables and Figures - House Style Guidelines

All tables and figures must be original for original research. If a table or figure has been published before, written permission must be given by the owner for its reproduction.

Tables

All tables must be cited in the text in the order that they should appear. Tables should be typed double-spaced on separate pages with number and title. Symbols for units should be confined to column headings. Tables must be supplied in an editable format. It is not acceptable to supply tables as images. You will be asked to resupply any table submitted in a non-editable format.

Figures

All figures must be cited in the text in the order that they should appear. Illustrations are an important medium through which to convey the meaning in your article, and there is no substitute for preparing these to the highest possible standard. Therefore, please create your illustrations carefully with reference to our graphics guidelines (see http://authorservices.wiley.com/bauthor/illustration.asp). It is very difficult to improve an image that has been saved or created in an inappropriate format. We realize that not everyone has access to high-end graphics software, so the following information may help if you are having difficulty in deciding how to get the best out of the tools at your disposal.

1. Check your software options to see if you can ‘save as’ or ‘export’ using one of the robust, industry-standard formats. These are:

- Encapsulated PostScript (EPS)
- Tagged Image File Format (TIFF)
- Portable Network Graphics (PNG)
- Portable Document Format (PDF)

2. As a general rule of thumb, images that contain text and line art (graphs, charts, maps, etc.) will reproduce best if saved as EPS or PDF. If you choose this option, it is important to remember to embed fonts. This ensures that any text reproduces exactly as you intend. 3. Images that contain photographic information are best saved as TIFF or PNG, as this ensures that all data are included in the file. JPEG (Joint Photographic Experts Group) should be avoided if possible, as information is lost during compression; however, it is acceptable for purely photographic subjects if the image was generated as a JPEG from the outset (many digital cameras, for example, output only in JPEG format). 4. If you

are not sure which format would be the best option, it is always best to default to EPS or PDF as these are more likely to preserve the high-quality characteristics of the original. 5. Microsoft Office. If you have generated your images in Microsoft Office software (Word, Excel, PowerPoint), or similar, it is often best simply to send us the files in their native file formats. 6. Please ensure all images are a minimum of 600 dpi.

Supporting Information

Supporting Information can be a useful way for an author to include important but ancillary information with the online version of an article. Examples of Supporting Information include additional tables, data sets, figures, movie files, audio clips, and other related nonessential multimedia files. Supporting Information should be cited within the article text, and a descriptive legend should be included. It is published as supplied by the author, and a proof is not made available prior to publication; for these reasons, authors should provide any Supporting Information in the desired final format.

For further information on recommended file types and requirements for submission, please visit: http://authorservices.wiley.com/bauthor/suppinfo.asp.

REVIEW PROCESS

Editorial and Peer Review Process

The Journal of Sexual Medicine maintains the highest standards of peer review and pursues editorial approaches that may help us avoid bias. All submitted manuscripts are reviewed for quality, novelty, scientific importance, and relevance to the journal's readership. Manuscripts with insufficient priority for publication or those that are outside the scope of the journal are rejected promptly, or, if appropriate, referred to *Sexual Medicine*. Manuscripts are assigned to an Associate Editor, who is a subject expert. Associate Editors select the external peer reviewers who are experts in the field, and submit a recommendation to the Editor-in-Chief along with the peer review reports. The Editor-in-Chief makes all final decisions on manuscripts. All research articles published in the journal undergo full peer review. We do our utmost to judge research objectively on its own merits and to avoid favoring research, for example, from particular institutions, countries, or regions. *The Journal of Sexual Medicine* employs a double-blind review process in which author identities and peer reviewer identities are kept confidential from one another. All publication decisions are made by the Editor-in-Chief on the basis of the reviews provided. Members of the Editorial Board lend insight, advice, and guidance to the Editor-in-Chief generally and assist in decision making on specific submissions. The Managing Editor and Editorial Assistant provide administrative support to ensure the journal maintains the integrity of peer review and delivers rapid and efficient publication to authors and reviewers. The existence of a manuscript under review is not revealed to anyone other than the peer reviewers and editorial staff. Peer reviewers are required to maintain confidentiality about the manuscripts they review and must not divulge any information about a specific manuscript or its content to any third party without prior permission from the journal editors. All

authors will be sent notification of the receipt of manuscripts and editorial decisions by e-mail. During the review process, designated contact authors can also check the status of the submitted manuscript via ScholarOne Manuscripts at http://mc.manuscriptcentral.com/jsm.

Information for Peer Reviewers

As per the guidelines issued by the World Association of Medical Editors (for further information, refer to www.WAME.org):

"Reviews will be expected to be professional, honest, courteous, prompt, and constructive. The desired major elements of a high-quality review should be as follows:

• The reviewer should have identified and commented on major strengths and weaknesses of study design and methodology.

• The reviewer should comment accurately and constructively upon the quality of the author's interpretation of the data, including acknowledgment of its limitations.

• The reviewer should comment on major strengths and weaknesses of the manuscript as a written communication, independent of the design, methodology, results, and interpretation of the study.

• The reviewer should comment on any ethical concerns raised by the study, or any possible evidence of low standards of scientific conduct.

• The reviewer should provide the author with useful suggestions for improvement of the manuscript.

• The reviewer's comments to the author should be constructive and professional.

• The review should provide the editor the proper context and perspective to make a decision on acceptance (and/or revision) of the manuscript."

Recommendations about publication are appreciated and are welcomed in the comments to the Editors. However, we kindly ask that reviewers not make such recommendations in their comments to the authors. Indeed, it is our policy to edit such comments out of any communications to authors.

CrossCheck

CrossCheck is a multi-publisher initiative to screen published and submitted content for originality. To find out more about CrossCheck visit http://www.crossref.org/crosscheck.html. By submitting your manuscript to *The Journal of Sexual Medicine* you accept that your manuscript may be screened, using the iThenticate tool, for textual similarity to other previously published works.

COPYRIGHT TRANSFER

Authors will be required to assign copyright in their papers. Copyright assignment is a condition of publication and papers will not be passed to the publisher for production unless copyright has been assigned. The copyright transfer agreement form is available here.

PRODUCTION PROCESS

Proofs

Soon after acceptance, you will receive an email containing your PDF proof. The corresponding author must return all proof corrections within 48 hours and limit changes to corrections of typographical errors and errors in the presentation of data. Once you have submitted your corrections, the production office will finalize the layout of your article for publication.

Reprints

Authors will receive instructions on how to purchase reprints inside their proof packets. Please note that regardless of the form in which they are received, reprints should not be resold, nor further disseminated in electronic form, nor deployed in part or in whole in any marking, promotional, or educational contexts without authorization from Wiley.

Production Questions

Please direct any questions regarding the production of your article to the Production Editor at syooi@wiley.com.

Author Resources

For additional tools visit Author Resources - an enhanced suite of online tools for *The Journal of Sexual Medicine* authors, featuring Article Tracking, E-mail Publication Alerts, and Customized Research Tools.

Embargo Policy

Once submitted, contributions cannot be discussed with the media until one week before the publication date. Accepted articles are embargoed from reporting by all media until 12:01 A.M. (EST) on the date of issue. Authors who discuss their work with the media prior to publication must ensure that the media representatives know the embargo policy and the embargo date. Authors arranging their own publicity on their articles are advised to notify *The Journal of Sexual Medicine* Editorial Office in advance. The Journal of Sexual Medicine does not provide embargo dates to authors arranging their own publicity.

SELF-ARCHIVING

Following publication of the final published version, the author retains the right to self-archive the submitted version on the author's personal website or in the author's institution's/employer's institutional repository or archive. This right extends to both intranets and the Internet. Authors may not self-archive on 3rd-party repositories. Authors may not update the submitted version or replace it

with the published version. The version posted must contain a legend as follows: This is the pre-peer-reviewed version of the following article: FULL CITE, which has been published in final form at [Link to final article]. Please see the Copyright Transfer Agreement for additional details on author rights.

NIH PUBLIC ACCESS MANDATE

The Journal of Sexual Medicine fully complies with the NIH public access mandate. For those interested in the Wiley policy on the NIH Public Access Mandate, please visit our policy statement.

GETTING HELP

If you need additional help, please contact the Managing Editor at jsm@issm.info.

Manuscript Submission Checklist

Please complete the following steps to ensure the correct submission of your manuscript:

- Include a title page for your manuscript that is separate from the rest of the main document (preferably uploaded as a Supplementary File Not for Review), including:

• Full author names and the highest qualifications (PhD, MD, etc.) for all authors;

• Institution, city and country details for each author; and,

• Address of corresponding author (especially email address for the person to whom the proof notification is to be sent).

- Please upload the main manuscript without identifying author information, including:

• Title page WITHOUT authors' names or authors' affiliations

• Abstract and 4–10 keywords

• Text (introduction, materials and methods, results, discussion)

• Literature cited (see below for tips on references)

• Tables (may be sent as a separate file if necessary)

• Figure legends

• Acknowledgements, including details of funding bodies with grant numbers

- Abstracts for Original Research articles must be structured as follows: Introduction, Aims, Methods, Main Outcome Measures, Results, Conclusion.
- Abstracts for Case Reports should be structured as follows: Introduction, Aims, Methods, Results, Conclusion.

- Provide a conflict of interest statement for every author.
- Please pay attention to the quality of all figures and artwork supplied (see below for requirements):

• All charts must be in black and white or grayscale.

• Should your figures originate in a PowerPoint presentation, please remove: any previous presentation effects, such as line-art color that is not of didactic value; background color or shading effects and 3-dimensional views where 2-d can convey results with equal effectiveness.

• All text included in figure labels must be of a sufficient size to be legible should the figure be resized during typesetting.

• Do not include the figure title or figure identification number within the figure itself. This does not reproduce effectively and typically does not fit journal style.

• Please save your figure files at the highest resolution possible. Please also supply figure art in original file formats whenever possible. Images imbedded in a MS Word document typically do not possess a resolution as high as the original file.

- Have all scientific symbols used in your manuscript transferred successfully to the PDF proof? Please correct this problem before submission.
- All references must be displayed sequentially based upon order of citation. References ordered alphabetically are not acceptable. Failure to comply with, or perform, these important tasks may delay both peer-review of your manuscript and its eventual publication.

REPRODUCTION PERMISSION

You can obtain permission to reproduce *The Journal of Sexual Medicine* content directly from the journal's website. Just search for the material you wish to reuse on Wiley Online Library. Click on the 'Request Permission' link.

• Follow the online instructions and select your requirements from the drop down options to gain a 'quick quote'

• Create a RightsLink® account to complete and pay for your transaction (if you do not already have one)

• Read and accept our Terms & Conditions and Download your license

COMMUNICATIONS TO THE PUBLISHER

For business inquiries, subscription information, orders, or subscriber changes of address, and all other information visit: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1743-6109/homepage/Contact.html.