Article | Open Access | Published: 29 July 2020

Different levels of estradiol are correlated with sexual dysfunction in adult men

Tong Chen, Fei Wu, Xianlong Wang, Gang Ma, Xujun Xuan, Rong Tang, Sentai Ding & Jiaju Lu

Scientific Reports **10**, Article number: 12660 (2020)

Abstract

Ejaculatory dysfunction, including premature ejaculation (PE) and delayed ejaculation (DE), as well as erectile dysfunction (ED), constitute the majority of male sexual dysfunction. Despite a fair amount of data on the role of hormones and erection and ejaculation, it is inconclusive due to controversy in the current literature. To explore the correlation of male sexual dysfunction with hormonal profile, 1,076 men between the ages of 19–60 years (mean: 32.12 years) were included in this retrospective case–control study; 507 were categorized as ED, PE and DE groups. Five hundred and sixty-nine men without sexual dysfunction were enrolled in the control group. The background characteristics and clinical features of the four groups were collected and analyzed. The estradiol value was significantly elevated in the ED group than the control group (109.44 ± 47.14 pmol/L vs. 91.88 ± 27.68 pmol/L; $P < 0.001$). Conversely, the DE group had significantly lower level of estradiol than control did (70.76 ± 27.20 pmol/L vs. 91.88 ± 27.68 pmol/L; $P < 0.001$). The PE group had similar level of estradiol (91.73 ± 31.57 pmol/L vs. 91.88 ± 27.68 pmol/L; $P = 0.960$) but significantly higher level of testosterone (17.23 ± 5.72 nmol/L vs. 15.31 ± 4.31 nmol/L; $P < 0.001$) compared with the control group. In conclusion, elevated serum testosterone concentration was an independent risk factor

for PE. Besides, there was a progressively increasing graded-distribution of estradiol values from DE to PE and ED groups.

Introduction

Sexual dysfunction is a common clinical entity worldwide and has a deleterious role in quality of life for the couple[1]. In men, erectile dysfunction (ED) and ejaculatory dysfunction are the most reported sexual dysfunction. According to the timing of ejaculation, ejaculatory dysfunction can be classified into premature ejaculation (PE) and delayed ejaculation (DE)[2]. ED is involved in pathophysiological alterations via neurogenic, psychoneurologic, vasculogenic, endocrine and iatrogenic pathways. In contrast, the etiology of ejaculatory dysfunction is under-reported and the understanding of hormonal control in ejaculatory dysfunction is still in its infancy.

Hormones can regulate many aspects of male reproduction. Endocrine disorders, including hypogonadism, thyroid diseases and hyperprolactinaemia, has been implicated in the pathogenesis of ED[3]. Testosterone is the major hormonal regulator of penile development and physiology, and affects both the central and peripheral levels of the ejaculatory process[1]. Aromatase is responsible for the conversion of testosterone to estrogen and localized abundantly in the male reproductive system. Levels of estradiol have been demonstrated to be correlated with the incidence and severity of ED[4], which could be explained by two hypotheses. One hypothesis is that the imbalance between estradiol and testosterone decreases the relaxation of cavernosal smooth muscle via an NO-mediated pathway[5]. The other hypothesis is that estrogen could antagonize the effect of testosterone through the sympathetic and parasympathetic nervous system, which in turn influence erectile function[6]. Apart from the effect on erectile function, estrogen also influences ejaculatory function. In mice, the expression pattern of estrogen receptor (ER) is unique throughout male reproductive tract other than the epididymis. In the epididymis, both ERα and ERβ are expressed[7]. In doing so, epididymal

contractility, critical for the first step of emission phase during ejaculation, is regulated by estradiol[8]. ERα or aromatase knockout male mice displayed decreased intromissions and ejaculations compared with wild-type controls[9,10]. In contrast to these findings, several case reports indicated that sexual behavior did not change in men lacking ERα or aromatase[11,12]. Therefore, the influence of ERα or aromatase in males remains controversial.

Collectively, despite a fair amount of data on the role of hormones and erection and ejaculation, it is inconclusive due to controversy in the current literature. Besides, no prior study has investigated the relationship between estradiol and ejaculatory dysfunction in men to date. We hypothesized that testosterone and estradiol might be involved in the regulation of erection and ejaculation in men. To investigate the correlation of hormonal profile with ED, PE, and DE, we conducted a retrospective case–control study with 1,089 men at our institution.

Materials and methods

Study population

Between May 2016 and April 2018, adult men with ED, PE or DE who firstly attended andrology clinic of the hospital were enrolled in the current study. Exclusion criteria were: untreated endocrine disorders, psychiatric disorder, anatomical penile abnormality, alcohol or drug abuse in the previous two years, and taking drugs (pseudoephedrine, antidopaminergics, testosterone preparations, serotonin reuptake inhibitors, and antihypo/hyperthyroidism drugs) which might influence intra-vaginal ejaculation latency time (IELT) or hormonal values. Participants were dissuaded from drinking alcohol before sexual intercourse. The coincidence of ED and PE is common in clinical practice, and patients with ED and PE were not taken into the present study. During the same period, subjects from the control group were randomly selected among participants without sexual dysfunction who carried out a health examination before undergoing in-vitro fertilization (IVF). Clinical features of the participants, including background information

and hormonal profile, were collected. The study protocol was approved by the ethical committee at Center for Reproductive Medicine, Shandong University. Informed consent was obtained from all participants for this study. Besides, all methods were carried out in accordance with relevant guidelines and regulations.

Assessment of ED, PE and DE

All participants possessed a stable, monogamous, heterosexual relationship with the partner, and the disease lasted for at least six months. The female partners of the subjects were proposed to apply a calibrated stopwatch to measure IELT. ED is the persistent inability to obtain or maintain an adequate erection to enable satisfactory sexual performance. A patient was diagnosed with ED when IIEF-5 score was smaller than 22[13]. During the screening period, the diagnosis of PE was confirmed when IELT results of sexual intercourse suggested a baseline IELT prior to or within one minute of vaginal penetration at least three times[14]. Furthermore, as the median IELT was 5.4 min in healthy men[2], the diagnosis of DE was confirmed when the baseline IELT was longer than 25 min (mean plus two standard deviations) and the patient ceased sexual activity due to irritation, exhaustion, partner request or erection loss[15].

Measurement of hormonal parameters

For the determination of the hormonal profile, participants with overnight fast were arranged in sitting posture for 30 min before sampling, and then blood samples were drawn from the antecubital veins between 8 and 10 am. Serum samples were analyzed for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), total testosterone (T), estradiol (E_2), and thyroid-stimulating hormone (TSH). When abnormal values appeared, a second sample of the blood was obtained for the re-assessment. The hormonal levels were investigated using the Cobas 6,000 analyzer series (Roche Diagnostics GmbH, Mannheim, Germany) in the laboratory department of the hospital. Among these hormones detected, serum estradiol levels were measured using Elecsys estradiol III kit (Roche Diagnostics Ltd., Shanghai, China). The lower and upper detection limits for estradiol were 28.0 and 156.0 pmol/L, respectively. In addition, the intra-assay

coefficient of variation was below 10%, and inter-assay coefficient of variation was below 15%.

Statistical analysis

We ran the data analysis using SPSS (version 22.0, Chicago, IL, USA) and two-sided *P* values < 0.05 were considered statistically significant. Data were assessed for normality using the Kolmogorov–Smirnov test. The population of the current study was categorized as four groups, namely, ED, PE, DE and control groups. The results were reported as mean ± standard deviation (SD) for continuous variables and number with percentage for categorical variables. One-way ANOVA followed by Student–Newman–Keuls post-hoc test was used to assess the continuous variables. Kruskal–Wallis method was applied for the analysis of skewed variables. The categorical variables were analyzed using Pearson χ^2 test. For the comparison of differences between two groups, means of normally distributed parameters were analyzed using Student's *t* test. The contribution of different variables to ED, PE and DE groups was determined using multivariable logistic regression. The odds ratio (OR) was explained as the measurement of correlation.

Results

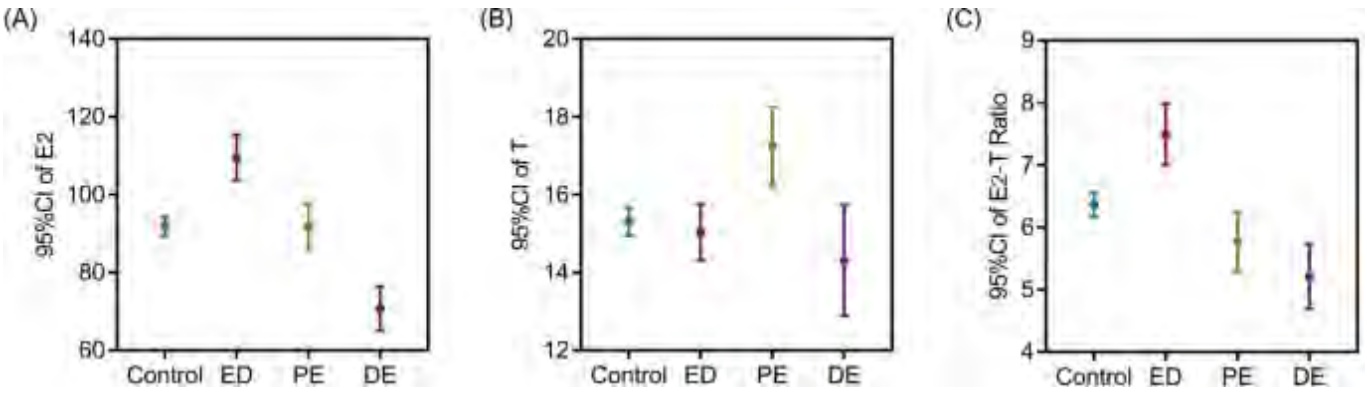
Patient characteristics and hormonal profile

Among 507 men with sexual dysfunction, 277 (53.1%) complained of ED, whereas 124 (23.8%) and 106 (20.3%) declared PE and DE, respectively. Besides, 569 men without sexual dysfunction were recruited in the control group. Table 1 indicates the baseline information of the participants. Figure 1 illustrates the means and 95% confidence interval (CI) of E_2, T and E_2-T ratio among control, ED, PE and DE groups, respectively. The comparison of hormonal profile among groups is summarized in Table 2. Testosterone values in the PE group were significantly higher than those in the control group (17.23 ± 5.72 nmol/L vs. 15.31 ± 4.31 nmol/L; $P < 0.001$). Furthermore, estradiol

levels were significantly higher for patients with ED (109.44 ± 47.14 pmol/L; $P < 0.001$), but significantly lower for patients with DE (70.76 ± 27.20 pmol/L; $P < 0.001$) compared with those in the control group (91.88 ± 27.68 pmol/L). The ED group had a significantly higher E_2-T ratio than control ($7.49 \pm 3.96 \times 10^{-3}$ vs. $6.37 \pm 2.41 \times 10^{-3}$; $P < 0.001$) did. Conversely, the E_2-T ratio was significantly decreased for patients with PE ($5.77 \pm 2.46 \times 10^{-3}$; $P = 0.021$) and DE ($5.21 \pm 2.42 \times 10^{-3}$; $P < 0.001$) than for patients in the control group ($6.37 \pm 2.41 \times 10^{-3}$).

Table 1 Background characteristics of the participants among groups.

Figure 1



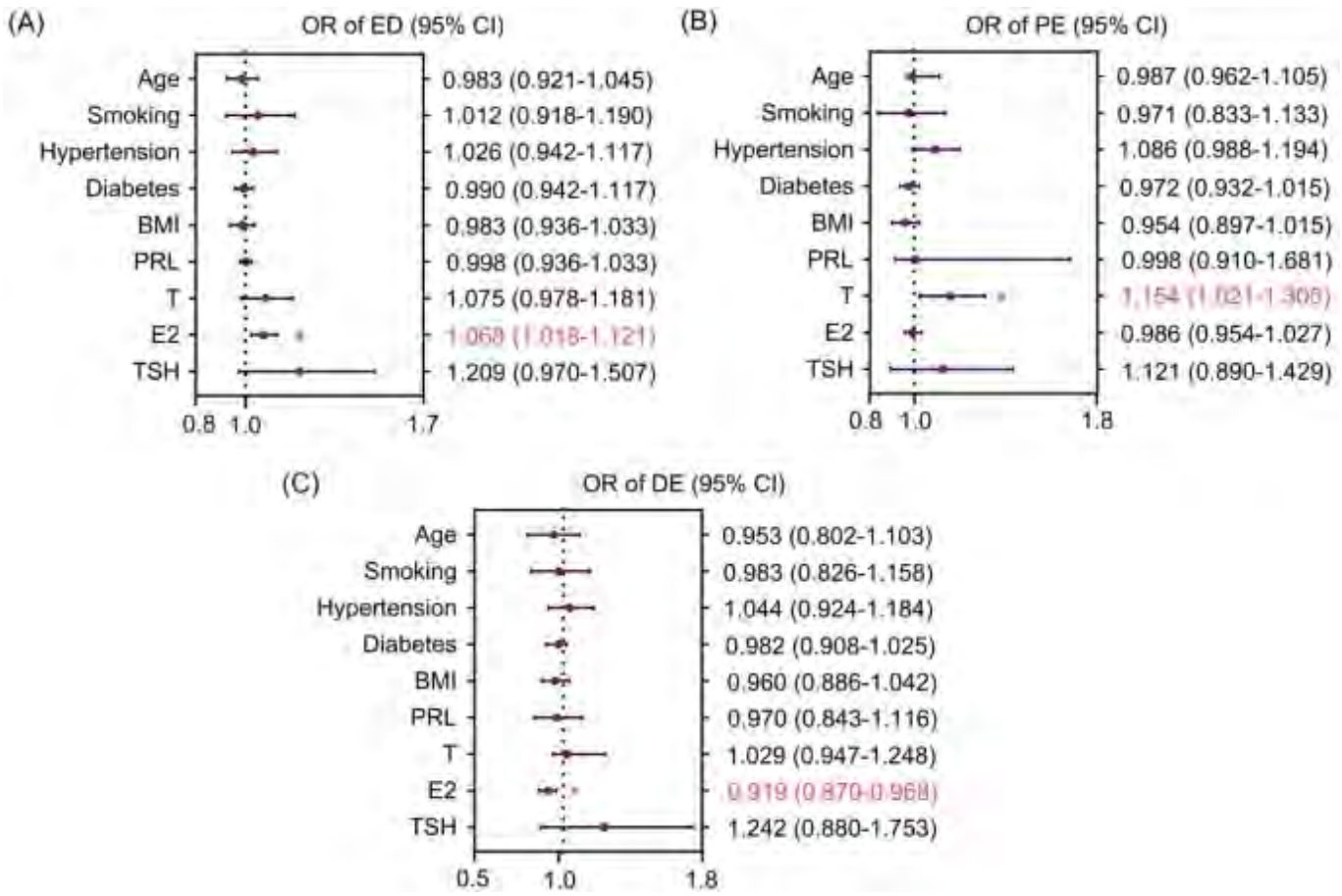
Error bar charts of E_2, T and E_2-T ratio among control, ED, PE and DE groups. (**A**) The means and 95% CI of E_2 among four groups; (**B**) The means and 95% CI of T among four groups; (**C**) The means and 95% CI of E_2-T ratio among four groups. E_2-T ratio: estradiol to testosterone ratio. *CI* confidence intervals.

Table 2 Hormonal profile of the participants among groups.

Independent risk factors for ED, PE and DE

Multivariable logistic regression analyses were conducted to explore the ORs for ED, PE or DE. In order to determine independent risk factors, age, BMI, smoking, hypertension, diabetes, testosterone, estradiol, TSH, and prolactin were considered as confounders in the regression models. Figure 2 shows the OR of ED, PE or DE group for controls as the reference. Estradiol was considered as an independent risk factor for ED and DE. Specifically, the OR of ED group versus controls was 1.068 (95% CI 1.018–1.121, $P<0.001$), and the OR of DE group versus controls was 0.919 (95% CI 0.870–0.968, $P<0.001$). Furthermore, testosterone was an independent risk factor for PE, and the OR of PE group versus controls was 1.154 (95% CI 1.021–1.305, $P<0.001$).

Figure 2

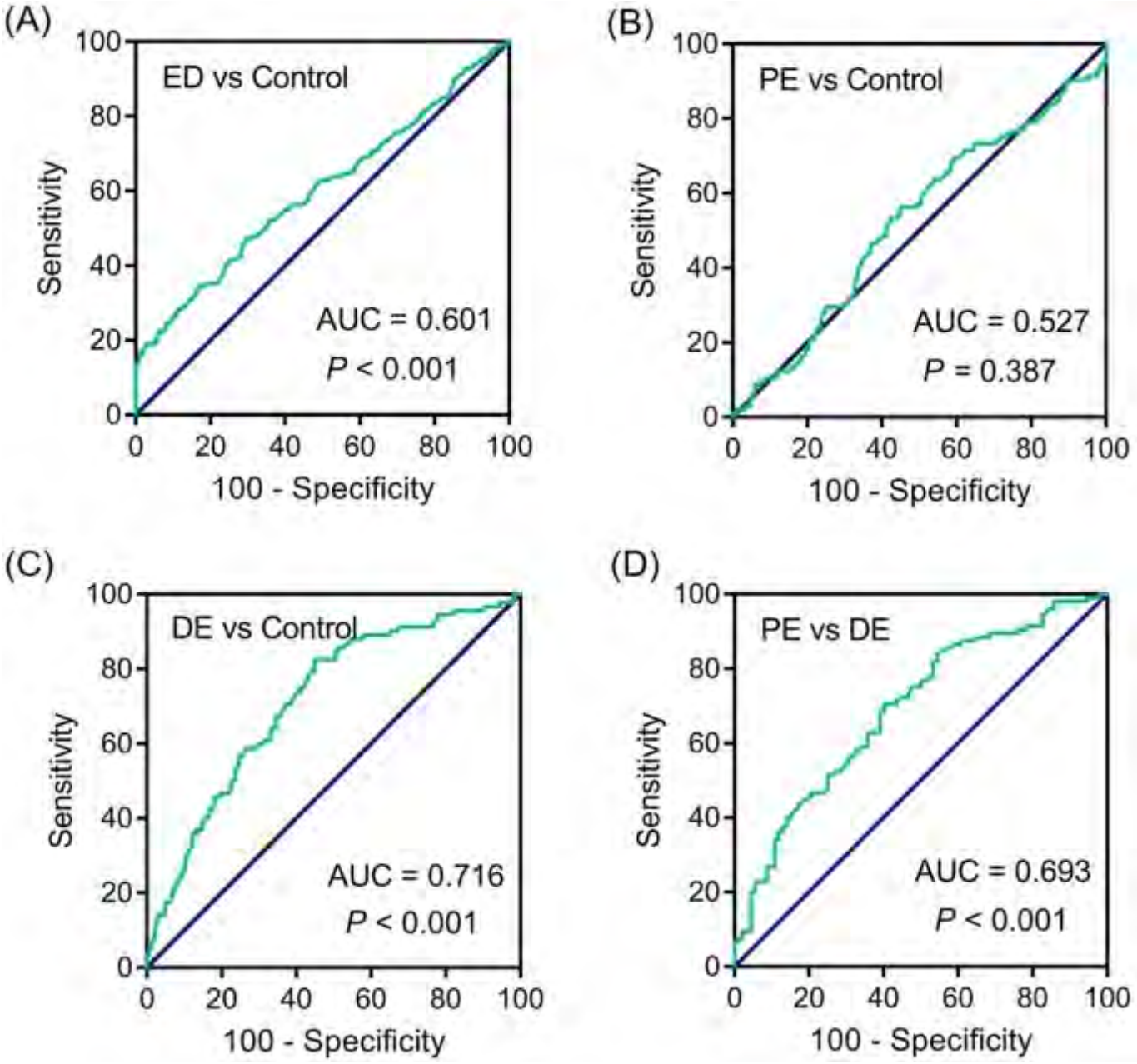


Risk for ED, PE and DE as estimated by different variables. (**A**) The OR of ED for normal controls as references; (**B**) The OR of PE for controls as references; (**C**) The OR of DE for controls as references. *OR* odds ratio; *CI* confidence interval.

Distinguishing ED, PE and DE using estradiol levels

As the mean level of estradiol was significantly different among groups, the diagnostic effect of the estradiol level for ED, PE, or DE was determined. The receiver operating characteristic (ROC) curve was used to explore area under the ROC curve (AUC) in every group using the estradiol values (Fig. 3). The AUC of ED group is 0.601 and the estradiol level of ED patients is significantly higher than that of men in the control group (Fig. 3A, SE: 0.023, 95% CI: 0.556–0.645, $P<0.001$). However, estradiol levels were unlikely to distinguish PE patients from normal cases (Fig. 3B, $P=0.387$). In addition, the AUC of the DE group is 0.716 (Fig. 3C, SE: 0.028, 95% CI: 0.661–0.771, $P<0.001$). Figure 3D indicates the significantly distinguishing ability of estradiol values between PE and DE groups (AUC = 0.693, SE: 0.037, 95% CI: 0.620–0.766, $P<0.001$).

Figure 3

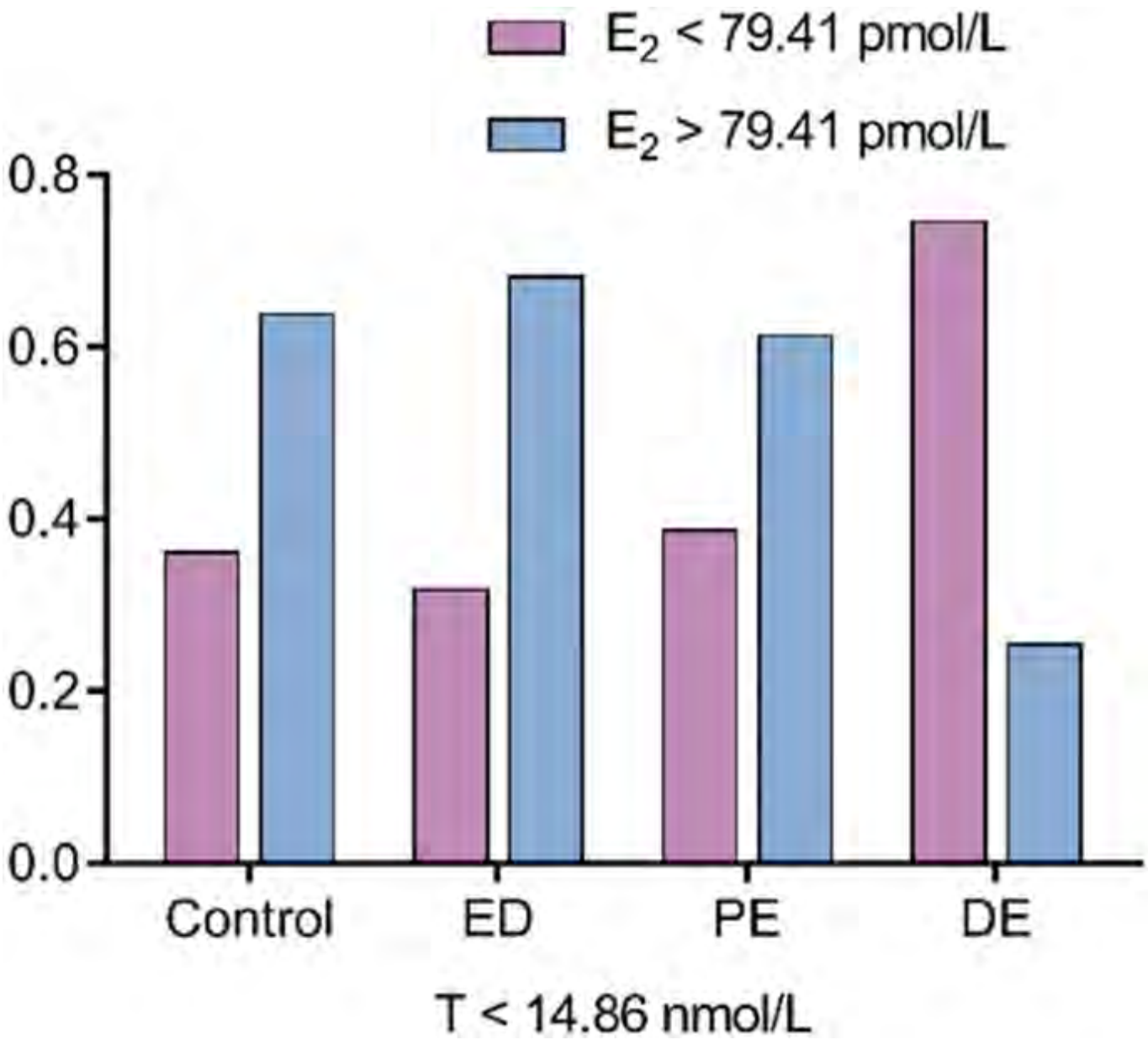


ROC curves of E_2 with values correlated with AUC. (**A**) The ROC curve of E_2 to diagnose ED; (**B**) The ROC curve of E_2 for to diagnose PE; (**C**) The ROC curve of E_2 to diagnose DE; (**D**) The ROC curve of E_2 to distinguish between PE and DE.

The best value to distinguish PE from DE was explored using ROC curve and AUC that was 14.86 nmol/L of testosterone (AUC: 0.671, SE: 0.036, 95% CI: 0.600–0.742, $P < 0.001$). Subjects with testosterone > 14.86 nmol/L were more likely to report PE compared with those with testosterone < 14.86 nmol/L (Sensitivity = 0.619, Specificity = 0.726). PE and DE subjects with testosterone < 14.86 nmol/L were further explored using

ROC curve followed by AUC of estradiol, and the best value was 79.41 pmol/L (Sensitivity = 0.741, Specificity = 0.613; AUC: 0.703, SE: 0.061, 95% CI: 0.584–0.823, $P < 0.001$). However, levels of estradiol were unlikely to distinguish DE from PE in these patients with testosterone > 14.86 nmol/L ($P = 0.058$). Therefore, we arranged all 528 cases with testosterone < 14.86 nmol/L into eight groups according to the crucial cutoff value of estradiol, and Fig. 4 illustrates the proportion of each group. For cases with testosterone < 14.86 nmol/L, it was likely for DE subjects to possess lower absolute value of estradiol, whereas the other subjects tended to have higher estradiol values.

Figure 4



The number of the participants in the four groups. All the participants with T < 14.86 nmol/L were then categorized as two groups based on E_2 of 79.41 pmol/L.

Discussion

Overall, our data indicated that significantly higher testosterone values were found in the PE group than in the control group. Levels of estradiol were significantly higher for ED patients, but significantly lower for DE patients when compared with control. The OR of DE was 0.919 for normal controls as the reference. Moreover, the OR of ED was 1.068 for normal controls as references. The best value to distinguish PE from DE was explored using ROC curve and AUC that was 14.86 nmol/L of testosterone.

The pathophysiological role of testosterone in ED has been extensively investigated. However, evidences on the correlation of testosterone levels with ED still remains controversial. Some studies documented that testosterone levels were not associated with ED[16,17], whereas others reported associations between definitely subnormal levels of testosterone and ED[18]. Our data demonstrated that no statistically significant differences were observed between ED and control groups. Furthermore, as hypothesized, ED was affected by high estradiol levels or the imbalance between estradiol and testosterone[19]. Men with higher estradiol levels had reduced spontaneous erections, decreased nocturnal penile tumescence and greater levels of psychological distresss[20]. In animal models by use of rabbits, increased estrogen levels were associated with ED[21], and the structure of corpus cavernosum was damaged by administration of exogenous estrogen[19]. The current study, with 88.39% of participants being younger than 40 years old, indicated that elevated estradiol levels were associated with ED in young men. Simultaneously, one interesting finding is that BMIs in the groups did not show a significant difference, but the estradiol level was significantly higher in the ED group. As the majority of aromotase is localized to lipid cells[22], it is plausible to assume that men with higher estradiol levels are those who are most obese and obesity has clearly been associated with ED[23,24]. To the best of our knowledge, body weight is

made up of the sum of fat and lean mass. In men with reduced muscle mass, excess body fat can occur within the normal BMI range. In addition, BMI does not take into account the accumulation of visceral fat that characterizes the most morbigenous form of obesity: central obesity. Waist circumference appears to be more suitable to explain obesity-related health risks than BMI[25]. Also, previous studies demonstrated that waist circumference was superior to BMI in predicting ED[23,24]. Therefore, the reasonable explanation is that the percent of men with central obesity in the ED group might have been higher compared with that in the other groups. Central obesity may not lead to an elevated BMI but can give rise to a higher estradiol level. Similar to our results, recent study reported that elevated estradiol level was significantly associated with ED independent of BMI[26].

The effect of testosterone on ejaculatory reflex could be explained by central, spinal and peripheral mechanisms[1]. In animal models, elevated testosterone levels decreased serotonin and its metabolite, contributing to PE[18]. Our results reported that PE patients had significantly higher levels of testosterone compared with control. Similar results were reported by other studies[27,28]. Yet, Patrick et al. found no association between PE and testosterone levels[29]. One possible explanation was that saliva samples, instead of blood samples, were applied to measure testosterone levels in Patrick's study[29]. Although some previous studies reported that low testosterone values were correlated with DE[27,28], there was no relationship between testosterone values and DE in the present study. This discrepancy could be illustrated by various populations and different eligibility criteria. One advantage of the current study was that the mean age of DE patients and normal controls were 32.19 and 32.33 years, respectively, eliminating the potential influence of aging on testosterone levels. In line with these observations, a recent prospective study reported that normal testosterone levels were found in most of the patients with DE[30]. It has been proposed that thyroid function and prolactin can modulate and interact with the male genital tract even within the normal range[31,32]. Besides, low level of prolactin is associated with a lessened ability to control ejaculation reflex[32]. However, our data demonstrated that there was no significant difference in levels of TSH or prolactin among the groups. Population-related differences might justify

this discrepancy, and the association between TSH or prolactin and ejaculatory disorders merits further investigation.

Although high estradiol milieu may adversely affect male sexual function, a moderate estradiol value is beneficial. Men with decreased estradiol levels reported low libido and sexual activity, which could be improved by estrogen administration[33]. Ramasamy et al. demonstrated that in men with decreased libido and testosterone levels below 300 ng/dl, libido was significantly improved when the estradiol level was over 5 ng/dl[34]. ERα, ERβ and aromatase were widely expressed in male genital tract[8]. Particularly, ERα and ERβ were abundantly localized in epididymal cauda, suggesting the role of estrogen in regulating epididymal function[1]. Specifically, in the emission phase during ejaculation, estrogen influences epididymal contractility, thus affecting the latency time[8]. Estradiol could revert hypogonadism-induced downregulation of RhoA/ROCK pathway and restore epididymal contractility[20]. In both rats and humans, ERα, ERβ and aromatase were profusely expressed in male brain, and masculinization of male brain is modulated by locally produced estrogen[20]. Estrogen can influence mood, mental state, cognition, and emotion through an interaction with serotonin receptors[20]. In men with aromatase deficiency, estrogen treatment enhances libido, sexual activity, and erotic fantasies[21]. Animal experiment revealed that aromatase inhibitors significantly reduce ejaculatory activity and sexual motivation, which could be improved by estradiol administration[20]. Decreased intromissions and no ejaculation were observed in ERα or aromatase knockout mice[9,10]. However, a man lacking ERα was reported to have no change in sexual behavior[12]. The current study indicated that estradiol values were significantly decreased for subjects in the DE group than for subjects in the control group. Due to anxiety, fear or attention deficit disorder, DE is characterized by disorders of arousal and sexual cues. Decreased estradiol values might lead to mood disorders before or during sexual intercourse. Also, the contractility of epididymis might be decreased in the setting of low estradiol levels. It was hypothesized that the expulsion phase was mediated by sympathetic excitation, whereas the emission phase was regulated by parasympathetic excitation[6]. In addition, sympathetic excitation might be modulated by estrogen, whereas parasympathetic sexual excitation might be dominated by testosterone[6]. Thus,

decreased estradiol values may attenuate the accumulation of sympathetic excitation, which in turn decelerate the expulsion process.

Our study has some limitations. First, estradiol levels in serum samples were not measured using mass spectrometry, which is considered the gold standard method for quantifying estradiol levels[29]. Second, SHBG was not determined, and thyroid function would be better assessed including free triiodothyronine (FT3) and free thyroxine (FT4)[31]. Third, ejaculatory function can be modulated by psychological characteristics to some extent[35,36], which was not evaluated in this study. Fourth, seminal/infertility status may play a role in male sexual dysfunction[35,37]. However, we did not evaluate seminal/infertility status of the included subjects. Fifth, our data did not include prostate inflammation, which may lead to an altered perception of the ejaculatory reflex and acquired PE[36,38]. Finally, some patients with ejaculatory dysfunction preferred self-reported perceived IELT rather than stopwatch measured IELT. Despite this, it should be noted that self-reported perceived IELT has been proved to be closely correlated with stopwatch measured IELT[39].

In conclusion, elevated serum testosterone level was an independent risk factor for PE. Moreover, there was a progressively increasing graded-distribution of estradiol values from DE to PE and ED groups.

References

1. Corona, G., Jannini, E. A., Vignozzi, L., Rastrelli, G. & Maggi, M. The hormonal control of ejaculation. *Nat. Rev. Urol.* **9**, 508 (2012).

2. MD, W. *et al.* A multinational population survey of intravaginal ejaculation latency time. *The journal of sexual medicine* **2**, 492–497 (2005).

3. O'connor, D. B. *et al.* The relationships between sex hormones and sexual function in middle-aged and older European men. *J. Clin. Endocrinol. Metab.* **96**,

E1577–E1587 (2011).

4. Schulster, M., Bernie, A. M. & Ramasamy, R. The role of estradiol in male reproductive function. *Asian J. Androl.* **18**, 435 (2016).

5. El-Sakka, A. I. Impact of the association between elevated oestradiol and low testosterone levels on erectile dysfunction severity. *Asian J. Androl.* **15**, 492 (2013).

6. Motofei, I. The etiology of premature ejaculation starting from a bihormonal model of normal sexual stimulation. *Int. J. Impot. Res.* **13**, 49 (2001).

7. Zhou, Q. *et al.* Localization of androgen and estrogen receptors in adult male mouse reproductive tract. *J. Androl.* **23**, 870–881 (2002).

8. Vignozzi, L. *et al.* Regulation of epididymal contractility during semen emission, the first part of the ejaculatory process: a role for estrogen (vol 5, pg 2010, 2008). *J. Sex. Med.* **5**, 2480–2480 (2008).

9. Ogawa, S., Lubahn, D. B., Korach, K. S. & Pfaff, D. W. Behavioral effects of estrogen receptor gene disruption in male mice. *Proc. Natl. Acad. Sci. USA* **94**, 1476–1481. https://doi.org/10.1073/pnas.94.4.1476 (1997).

10. Bakker, J., Honda, S., Harada, N. & Balthazart, J. Restoration of male sexual behavior by adult exogenous estrogens in male aromatase knockout mice. *Horm. Behav.* **46**, 1–10 (2004).

11. Chen, Z. *et al.* Aromatase deficiency in a Chinese adult man caused by novel compound heterozygous CYP19A1 mutations: Effects of estrogen replacement therapy on the bone, lipid, liver and glucose metabolism. *Mol. Cell. Endocrinol.* **399**, 32–42 (2015).

12.

12. Smith, E. P. *et al.* Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N. Engl. J. Med.* **331**, 1056–1061. https://doi.org/10.1056/nejm199410203311604 (1994).

13. Rosen, R. C. *et al.* The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* **49**, 822–830 (1997).

14. Se, A. *et al.* An update of the International Society of Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). *J. Sex. Med.* **11**, 1392–1422 (2014).

15. McMahon, C. G., Jannini, E., Waldinger, M. & Rowland, D. Standard operating procedures in the disorders of orgasm and ejaculation. *J. Sex. Med.* **10**, 204–229 (2013).

16. Rhoden, E. L., Teloken, C., Sogari, P. R. & Souto, C. A. V. The relationship of serum testosterone to erectile function in normal aging men. *J. Urol.* **167**, 1745–1748 (2002).

17. Kupelian, V. *et al.* Is there a relationship between sex hormones and erectile dysfunction? Results from the Massachusetts Male Aging Study. *J. Urol.* **176**, 2584–2588 (2006).

18. Rastrelli, G., Corona, G. & Maggi, M. Testosterone and sexual function in men. *Maturitas* **112**, 46–52 (2018).

19. Yafi, F. A. *et al.* Erectile dysfunction. *Nat. Rev. Dis. Primers* **2**, 16003 (2016).

20. Cooke, P. S., Nanjappa, M. K., Ko, C., Prins, G. S. & Hess, R. A. Estrogens in male physiology. *Physiol. Rev.* **97**, 995 (2017).

21. **21.** Vignozzi, L. *et al.* Estrogen mediates metabolic syndrome-induced erectile dysfunction: a study in the rabbit. *J. Sex. Med.* **11**, 2890–2902 (2014).

22. Longcope, C., Kato, T. & Horton, R. Conversion of blood androgens to estrogens in normal adult men and women. *J. Clin. Invest.* **48**, 2191–2201. https://doi.org/10.1172/jci106185 (1969).

23. TS, H. *et al.* Impaired quality of life and sexual function in overweight and obese men: the European Male Ageing Study. *Eur. J. Endocrinol.* **164**, 1003–1011. https://doi.org/10.1530/eje-10-1129 (2011).

24. Janiszewski, P. M., Janssen, I. & Ross, R. Abdominal obesity and physical inactivity are associated with erectile dysfunction independent of body mass index. *J. Sex. Med.* **6**, 1990–1998. https://doi.org/10.1111/j.1743-6109.2009.01302.x (2009).

25. Sa, T. & Ac, H. Waist circumference predicts increased cardiometabolic risk in normal weight adolescent males. *Int. J. Pediatric Obesity* **6**, e307-311. https://doi.org/10.3109/17477166.2011.575149 (2011).

26. Zuniga, K. B., Margolin, E. J., De Fazio, A., Ackerman, A. & Stahl, P. J. The association between elevated serum oestradiol levels and clinically significant erectile dysfunction in men presenting for andrological evaluation. *Andrologia* **51**, e13345. https://doi.org/10.1111/and.13345 (2019).

27. Corona, G. *et al.* Premature and delayed ejaculation: two ends of a single continuum influenced by hormonal milieu. *Int. J. Androl.* **34**, 41–48 (2011).

28. Corona, G. *et al.* Different testosterone levels are associated with ejaculatory dysfunction. *J. Sex. Med.* **5**, 1991–1998 (2010).

29.

29. Jern, P. *et al.* Associations between salivary testosterone levels, androgen-related genetic polymorphisms, and self-estimated ejaculation latency time. *Sex. Med.* **2**, 107–114 (2014).

30. Paduch, D. A. *et al.* Clinical and demographic correlates of ejaculatory dysfunctions other than premature ejaculation: a prospective, observational study. *J. Sex. Med.* **12**, 2276–2286 (2015).

31. Lotti, F. *et al.* Is thyroid hormones evaluation of clinical value in the work-up of males of infertile couples?. *Hum. Reprod.* **31**, 518–529. https://doi.org/10.1093/humrep/dev338 (2016).

32. Lotti, F. *et al.* Clinical implications of measuring prolactin levels in males of infertile couples. *Andrology* **1**, 764–771. https://doi.org/10.1111/j.2047-2927.2013.00114.x (2013).

33. Finkelstein, J. S. *et al.* Gonadal steroids and body composition, strength, and sexual function in men. *N. Engl. J. Med.* **369**, 1011–1022 (2013).

34. Ramasamy, R., Kovac, J. R., Scovell, J. M. & Lipshultz, L. I. Words of wisdom. Re: In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *Eur. Urol.* **65**, 844 (2014).

35. Lotti, F. & Maggi, M. Sexual dysfunction and male infertility. *Nat. Rev. Urol.* **15**, 287–307. https://doi.org/10.1038/nrurol.2018.20 (2018).

36. Lotti, F. *et al.* Clinical correlates of erectile dysfunction and premature ejaculation in men with couple infertility. *J. Sex. Med.* **9**, 2698–2707 (2012).

37.

Bǒtti, F. *et al.* Semen quality impairment is associated with sexual dysfunction according to its severity. *Hum. Reprod.* **31**, 2668–2680. https://doi.org/10.1093/humrep/dew246 (2016).

38. Lotti, F. *et al.* Seminal, clinical and colour-Doppler ultrasound correlations of prostatitis-like symptoms in males of infertile couples. *Andrology* **2**, 30–41. https://doi.org/10.1111/j.2047-2927.2013.00156.x (2014).

39. Rosen, R. C. *et al.* Correlates to the clinical diagnosis of premature ejaculation: results from a large observational study of men and their partners. *J. Urol.* **177**, 1059–1064. https://doi.org/10.1016/j.juro.2006.10.044 (2007) (**(Discussion 1064)**).

Acknowledgements

The authors gratefully acknowledge Linlin Tian from Department of Microbiology, Faculty of Basic Medical Sciences, Guilin Medical University for the proof reading of this manuscript. The study has been given the grant from Shandong Province Key Research and Development Program (No. 2017GSF218070).

Author information

1. These authors contributed equally: Tong Chen and Fei Wu.

Affiliations

1. Department of Urology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324 Jingwu Road, Jinan, 250021, Shandong, People's Republic of China

Tong Chen, Fei Wu, Sentai Ding & Jiaju Lu

2. Center for Reproductive Medicine, National Research Center for Assisted Reproductive Technology and Reproductive Genetics, The Key Laboratory for Reproductive Endocrinology of Ministry of Education, Shandong University, Jinan, 250021, Shandong, People's Republic of China

Tong Chen, Xianlong Wang, Gang Ma, Xujun Xuan, Rong Tang & Jiaju Lu

3. Department of Pediatric Surgery, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai, 200062, People's Republic of China

Tong Chen

4. Department of Urology, Shandong Provincial Qianfoshan Hospital, Jinan, 250002, Shandong, People's Republic of China

Fei Wu

Contributions

Study design: J.J.L. and S.T.D. Collection and analysis of data: T.C., F.W., X.L.W., and G.M. Manuscript writing: T.C., F.W., X.J.X., and R.T.

Corresponding author

Correspondence to Jiaju Lu.

Ethics declarations

Competing interests

The authors declare no competing interests.

Additional information

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Rights and permissions

About this article

Cite this article

Chen, T., Wu, F., Wang, X. *et al.* Different levels of estradiol are correlated with sexual dysfunction in adult men. *Sci Rep* **10,** 12660 (2020). https://doi.org/10.1038/s41598-020-69712-6

Received 31 January 2020 **Accepted** 08 July 2020 **Published** 29 July 2020

DOI https://doi.org/10.1038/s41598-020-69712-6

Share this article

Anyone you share the following link with will be able to read this content:

Get shareable link

Provided by the Springer Nature SharedIt content-sharing initiative

Subjects Sexual dysfunction • Urogenital diseases

Scientific Reports ISSN 2045-2322 (online)

ED: NON-HORMONAL CAUSES
Handout/Protocol

LIFESTYLE AND HABITS THAT CAUSE ED—Things You Never Think Of !

There are many habits of daily life that a man might participate in that can cause ED. There are no warning labels to tell you that these habits, activities and substances are dangerous to your sex life, but I have accumulated a list from my experiences talking to patients and their wives about everyday activities that cause a man to lose his ability to have sex. Sadly this is usually after I have investigated every medical reason for their problem and thrown up my hands.

Jerry and the Monster that caused ED!

Jerry is a 47 year old plumber who came to me for ED and lack of sex drive. He had a low free testosterone and several other minor medical issues that could affect his ability to get and keep a rigid erection. He was obviously fit with well-defined muscles despite his low free T, which is not typical of my patient's pre pellet body type. I decided to treat him with pellets after unsuccessfully attempting to increase his free T and lower his estrogens with Arimidex.

He was very motivated to get better because he and his wife had always had a very active sex life, sometimes having sex more than once a day. The loss of this form of communication with his wife was damaging his marriage.

Finally after several office visits I had exhausted all of my "tricks" to resolve his ED problem when his wife suggested a weird habit that he had that might "mean something"; He drank "Monster" caffeine drinks all day long, and then took a highly caffeinated power before he worked out every night. When he got home he could not perform! Eureka! That was the problem---Caffeine!

Caffeine is a vasoconstrictor, and when taken in large amounts (Monster Energy drink has 160 mg/can), and his energy power had 360 mg of caffeine per dose, causes impotence. Remember that an erection requires dilation of the blood vessels to become rigid. Caffeine does the opposite, and constricts blood vessels. Some men are more sensitive to caffeine than others, but one of the first things that a man should do when faced with this problem is wean off caffeine!

Over the next 2 months Jerry weaned off all caffeine except 2 cups of coffee a day, and voila, his erections were back! Remember if you do this, caffeine withdrawal is a painful process, so do it slowly!

PS. His lack of sex drive was not a lack of T but came from fear that he would not be able to perform!

Other Vasoconstrictors contained in foods and drugs that you may not think of.
If you have high blood pressure these substances can be deadly!

Vasoconstrictors That Can Cause ED

- **Caffeine**
- **Nicotine**
- **Sudafed, pseudoephedrine**
- **Cold medications, antihistamines**
- **Asthma medications and inhalers**
- **Methylphenidate**
- **Green tea**
- **ADD medicines-amphetamines**
- **Diet pills-over the counter and prescription-all of them**
- **Cocaine**
- **Epinephrine/adrenaline**
- **Adrenal supplements**
- **Phenylephrine**
- **Dopamine**
- **Angiotensin**
- **Atherosclerosis**
- **High Blood pressure**
- **Chronic stress**

Remember the words of your science teacher in high school? "For every action there is an equal and opposite reaction", and in the world of substances and drugs it is the same. If you want to improve your erection then you can employ substances and medications that relax blood vessels.

Vasodilators that Can Help Treat ED

- **Nitric oxide (Neo 40 -supplement)**
- **Viagra, Levitra, Cialis**
- **Magnesium supplement**
- **L-arginine and ornithine**
- **Diazoxide**
- **Minoxidil**
- **Retigabine- anti-seziure**
- **flupirtine**
- **Nitroglycerine**
- **Exercise**
- **Deep Breathing and Yoga**

BLOOD PRESSURE MEDICINE

Yes, high blood pressure and low blood pressure can cause ED, so the blood pressure medicine you take is very important, and must leave you with a normal pressure, not one that is too low (less than 110/70).

The *best blood pressure medications* to take are (ARBs-angiotensin Receptor Blockers) Benecar® (olmesartan) and (Calcium Channel Blockers) Cardizem® (diltiazem).

The *worst blood pressure drugs for your ED* is Lisinopril ® (angiotensin converting enzyme inhibitor or ACE inhibitor) and Metoprolol ® Procardia® and nifedipine (Beta Blockers). Diuretics like HCTZ (hydrochlorothiazide), Lasix® (furosemide) and Maxide® also lower blood volume and can decrease erection firmness and longevity. I feel obligated to emphasize that if the only blood pressure medication that you respond to is one of these, then it is more important to control your blood pressure, and you can add Viagra or other meds to help with your ED.

ANTI-INFLAMMATORY MEDS: MOTRIN, ADVIL, HYDROCORTISONE, AND ANTI-PROSTAGLANDINS

We all take anti-inflammatory drugs over the counter and prescription medications to treat aches and pains, but high dosage and daily dosing, and prescription anti-inflammatory medications can decrease the prostaglandins necessary to create an erection.
This effect is rarely the primary drug causing ED, but it may contribute. You can skip a dose if you are anticipating having sex.

DRUGS AND ED

By drugs, I mean illicit or illegal drugs that are obtained without a prescription from the doctor's office. The categories are THC (Marijuana), Cocaine/Ecstacy/Meth , Heroin and Morphine. All of these drugs decrease your ability to either get an erection or have a sex drive. If you want to keep your sex life intact then avoid these addictive drugs (not THC).

DEHYDRATION – Your "tank" must be full to get an erection!

Blood volume must be close to normal to get an erection. That means that you must drink *water, or non-caffeinated liquids* to fill up your blood volume "tank"
if you want to get an erection. You can become dehydrated if you drink alcohol, fly, sweat, or exercise so pay attention to life activities prior to scheduling sex!

Exercise is good for you, lowers blood pressure and dilates your blood vessels but you must provide enough blood volume to avoid ED. That means that 8 - 8 ounce glasses of water a day if you are not doing anything physical, and double that if you

are exercising. Not only do you need to replace water if you are exercising, but electrolytes salt and potassium are necessary so the product G2 is a wise choice to replenish your body during exercise.

STRESS Can Decrease Both Your Sex Drive And Your Ability To Perform

Stress of modern life is unavoidable however long working hours, fear for your ability to support yourself or your family, or constant intrusion of messages and phone calls can increase your cortisol, estrone and adrenalin and these hormones bind up your testosterone and counteract your erections.

It is important to have time to yourself where you can relax and enjoy life. Find out what activity allows you to relax and have fun and schedule it into your day. Aerobic exercise, weight lifting, stretching, yoga, reading sitting and watching TV or golf are all ways you can chill your adrenal gland out and get your sex life back on track.

SEDENTARY Lifestyle—Will Counteract Testosterone and cause ED

Most of us currently use our brains more than our bodies, so we sit around making fat out of our food and fat makes estrogen. In men too much estrogen counteracts testosterone and results in impotence. The fatter a man is, the worse this gets!

Another outcome of sedentary lifestyle is that we don't use our muscles enough and therefore inhibit blood flow everywhere and there is a decrease in nitric oxide. We can't just sit everyday and expect to have a great sex life!

Veganism—lack of animal protein

I am not a fan of veganism, not just because I am a confirmed omnivore (eats everything), but because in my experience my vegan patients do not have the education as to what they need to eat every day to provide their bodies with vital proteins required for their bodies to function. Those men who are vegans and are not obsessive about the amount of plant protein they take in to replace meat, cheese, eggs and other animal products that provide amino acids for bodily functions, end up without the muscle mass and hormones (all stimulatory hormones to every gland are made of proteins), and ED can come from lack of NO (Nitrous Oxide which comes from meat proteins.

Rarely have I found that veganism is properly done, but even then muscle mass is low and weak without the building blocks of animal proteins. The worst form of veganism is that type that consists of a salad every day and all the junk food you can ingest! For adequate sex hormones and nitric oxide you will need to ingest eggs, cheese and some meat.

SMOKING (NICOTINE)- SMOKING CAN KILL YOU AND YOUR SEX LIFE

Tobacco contains nicotine a vasoconstrictor, and creates hypoxia (lack of oxygen) throughout your body. A pack of cigarettes is equal to one cigar, so you can't deny that you are a smoker if you smoke cigars! I have seen several long term smokers that continued to smoke against all warnings and then were angry that they were completely impotent, such that Viagra doesn't work. That is what smoking does, besides requiring you to give up physical hobbies you love, and make you immobile. Stop before it is too late, to save your sex life, if the fear of losing your whole life hasn't motivated you yet!

4/18
KCM

Extra information Male Sexual Dysfunction

Male Sexual Dysfunction
Erectile Dysfunction Etiology

- Testosterone deficiency
- Vascular compromise, arteriosclerosis, low blood pressure, dehydration.
- Medications that interfere:
  - Antihypertensives
  - Diuretics
  - Finasteride
  - Beta Blockers
  - Alpha adrenergic blockers
- Anti-prostaglandins
- Penile scar tissue

- Morgentaler, Abraham, *Testosterone for Life, c. 2009, p. 33,44-58,81-83.*

Testosterone is Critical to Men's Erections and Libido

In Two Ways:

#1. T stimulates the sexual centers of the brain--→ convert arousing thoughts and sensations into nervous stimulation to dilate blood vessels.

#2. Testosterone directly stimulates the T receptors in the penile corpora cavernosa to create chemicals that bring about an erection.

Morgentaler, Abraham, *Testosterone for Life, c. 2009, p. 33,44-58,81-83.*

Neuro-transmitters and Receptors involved in Erections

- Adrenergic nerves secrete Noradrenaline (NA) receptors that stimulate sympathetic contraction
- NA is the main neurotransmitter controlling tumescence
- Parasympathetic nerves secrete Acetylcholine resulting in smooth muscle relaxation of arteries, cavernosal smooth muscle
- Nitric oxide (NO) is the primary neurotransmitter resulting in an erection.
- There is an alternating stimulation of the sympathetic and parasympathetic nerves to maintain erection

PSA Special Instructions

- It is a screening test
- Avoid sex and prostate exam, riding a bike and hot tubs for 72 hours before test
- If abnormal then order Total and Free PSA
- If still abnormal refer for exam to Urologist
- Some men maintain high PSAs from
  - Infection-prostatitis
  - Other systemic infections
  - Allopurinol
  - BP medication-minoxidil orally

Erectile Function:
Other neuro-transmitters include..

- Vasoacticve Peptide (VIP)
- Calcitonin gene-related peptide (CGRP)
- Prostaglandins
- Other Peptides

JAMA Neurology | Original Investigation

Association of Concussion Symptoms With Testosterone Levels and Erectile Dysfunction in Former Professional US-Style Football Players

Rachel Grashow, PhD, MS; Marc G. Weisskopf, PhD, ScD; Karen K. Miller, MD; David M. Nathan, MD; Ross Zafonte, DO; Frank E. Speizer, MD; Theodore K. Courtney, MS; Aaron Baggish, MD; Herman A. Taylor, MD; Alvaro Pascual-Leone, MD, PhD; Lee M. Nadler, MD; Andrea L. Roberts, PhD

IMPORTANCE Small studies suggest that head trauma in men may be associated with low testosterone levels and sexual dysfunction through mechanisms that likely include hypopituitarism secondary to ischemic injury and pituitary axonal tract damage. Athletes in contact sports may be at risk for pituitary insufficiencies or erectile dysfunction (ED) because of the high number of head traumas experienced during their careers. Whether multiple symptomatic concussive events are associated with later indicators of low testosterone levels and ED is unknown.

OBJECTIVE To explore the associations between concussion symptom history and participant-reported indicators of low testosterone levels and ED.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study of former professional US-style football players was conducted in Boston, Massachusetts, from January 2015 to March 2017. Surveys on past football exposures, demographic factors, and current health conditions were sent via electronic and postal mail to participants within and outside of the United States. Analyses were conducted in Boston, Massachusetts; the data analysis began in March 2018 and additional analyses were performed through June 2019. Of the 13 720 male former players eligible to enroll who were contacted, 3506 (25.6%) responded.

EXPOSURES Concussion symptom score was calculated by summing the frequency with which participants reported 10 symptoms, such as loss of consciousness, disorientation, nausea, memory problems, and dizziness, at the time of football-related head injury.

MAIN OUTCOMES AND MEASURES Self-reported recommendations or prescriptions for low testosterone or ED medication served as indicators for testosterone insufficiency and ED.

RESULTS In 3409 former players (mean [SD] age, 52.5 [14.1] years), the prevalence of indicators of low testosterone levels and ED was 18.3% and 22.7%, respectively. The odds of reporting low testosterone levels or ED indicators were elevated for previously established risk factors (eg, diabetes, sleep apnea, and mood disorders). Models adjusted for demographic characteristics, football exposures, and current health factors showed a significant monotonically increasing association of concussion symptom score with the odds of reporting the low testosterone indicator (highest vs lowest quartile, odds ratio, 2.39; 95% CI, 1.79-3.19; $P < .001$). The ED indicator showed a similar association (highest quartile vs lowest, odds ratio, 1.72; 95% CI, 1.30-2.27; $P < .001$).

CONCLUSIONS AND RELEVANCE Concussion symptoms at the time of injury among former football players were associated with current participant-reported low testosterone levels and ED indicators. These findings suggest that men with a history of head injury may benefit from discussions with their health care clinicians regarding testosterone deficiency and sexual dysfunction.

JAMA Neurol. 2019;76(12):1428-1438. doi:10.1001/jamaneurol.2019.2664
Published online August 26, 2019.

Author Audio Interview

Supplemental content

CME Quiz at jamanetwork.com/learning

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Rachel Grashow, PhD, MS, Department of Environmental Health, Harvard T. H. Chan School of Public Health, 655 Huntington Ave, Bldg 1, Ste 1402, Boston, MA 02215 (rgrashow@hsph.harvard.edu).

Healthy sexual function is important for psychosocial well-being[1,2] and intimate partner relations.[3,4] *Erectile dysfunction* (ED), defined as the inability to maintain an erection sufficient for sexual activity,[5] and pituitary hormone deficiencies may be long-term sequelae of traumatic brain injury (TBI).[6] A plausible biological mechanism for such effects is trauma-induced pituitary damage, which may lead to insufficiencies in testosterone, growth hormone, or cortisol levels,[7,8] termed *posttraumatic hypopituitarism*.[9-11]

Studies on sexual function in participants with brain injuries have reported a reduced frequency of intercourse,[10,12-14] diminished libido,[10,12-19] impaired ability to orgasm,[10,12,13,18,19] ED,[6,10,13-15,17] and sexual arousal issues.[10,12,18] However, these studies were conducted in clinical settings,[6,9,10,12-19] many were small (N < 100)[9,13-15,17,19] or did not specifically investigate ED.[12,16,18,19] Only 1 large study examined ED subsequent to a single TBI in 73 000 clinical patients and 218 000 controls.[6] Over a 10-year follow-up, the adjusted hazard ratio for ED in patients with TBI was 2.5 compared with participants without injuries, and greater TBI severity was associated with higher risk of ED.[6] However, this study focused only on medically evaluated single head injuries, rendering results less applicable to often underdiagnosed sports-related head traumas.[20,21] Furthermore, this study did not evaluate dose-response associations with repeated head injuries and lacked covariate data, such as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared).[22]

Limited research has been conducted on populations likely to receive repeated head injuries, such as athletes in combative and contact sports or the military. Small studies of professional boxers have found hormone insufficiencies[23-25] and smaller pituitary volumes[23] when compared with controls. One study of 68 National Football League (NFL) players with poor quality-of-life scores found significant associations between repeated mild head injury and pituitary and sexual dysfunction.[26] Three small studies (all N < 40) reported that veterans with mild blast-related head injury were more likely to have a pituitary hormone insufficiency compared with civilians and uninjured veterans.[27-29] Exploring these end points in professional US-style football players could yield new insights given that prior studies were small, looked only at clinically defined single head injuries, were conducted in players with a low quality of life, or were conducted in veterans with blast-related rather than mechanical trauma.

We examined the association between football-related concussion symptoms at the time of football injury and self-reported medication recommendations for low testosterone levels or ED in a large cohort of former professional US-style football players. Because former players are at increased risk for ED comorbidities, such as sleep apnea,[30,31] cardiometabolic disease,[32-34] opioid use,[35] depression,[30,36-41] obesity,[30] and prior use of performance enhancing drugs,[42] we conducted analyses further adjusted for these factors.

Key Points

Question Are professional US-style football players with a history of multiple concussion symptoms more likely to report indicators of low testosterone levels or erectile dysfunction (ED)?

Findings In this cross-sectional study of 3409 former players, a monotonically increasing association was found between the number of concussion symptoms and the odds of reporting an indicator of low testosterone level and ED.

Meaning Concussion symptoms among former football players were associated with low testosterone levels and ED indicators, suggesting that men with a history of head injury may benefit from discussions with their health care clinicians regarding these treatable outcomes.

Methods

Participants

The Football Players' Health Study (FPHS)[43] recruited men who played for the NFL after 1960, when the adoption of hard plastic helmets was mostly complete. Of the 14 906 player addresses obtained from the NFL Players' Association, 1186 (8.6%) were invalid. Questionnaires were sent to the remaining 13 720 former players, of whom 3506 (25.6%) had responded as of March 2017. The Beth Israel Deaconess Medical Center institutional review board approved this study. Informed written consent was obtained from all participants prior to participation.

Concussion Symptoms

Respondents were asked: "While playing or practicing football, did you experience a blow to the head, neck, or upper body followed by any of the following: headaches, nausea, dizziness, loss of consciousness (LOC), memory problems, disorientation, confusion, seizure, visual problems, or feeling unsteady on your feet?" Response options were: none, once, 2 to 5 times, 6 to 10 times, or 11 times or more for each symptom.

Outcomes

Respondents were asked "Has a medical provider ever recommended or prescribed medicine for: (1) low testosterone or (2) ED?" An affirmative answer served as an indicator of a history of low testosterone levels or ED, respectively. Participants reporting that a health care clinician had ever recommended or prescribed medication for either outcome were considered cases. Participants were additionally asked whether they currently took medication for low testosterone levels or ED.

Covariates

Participants chose the category that best described their race/ethnicity and were categorized by investigators as black, white, or other. Football position may be a proxy for training regimen, nutrition, and other unmeasured variables and has been associated with injuries.[44-47] Respondents provided the position(s) played most frequently, which included defensive back, defensive line, kicker/punter, linebacker, offensive line, quarterback, running back, special teams, tight end, or wide receiver. Respondents who selected "special teams" in addition to strength-based positions (eg, offensive line, defensive line, or tight end) were assigned "special line."[48] Players who selected "special teams" and speed-based positions (eg, running back, wide receiver, defensive back, or linebacker) were assigned to "special speed." For the 1037 players (29.6% of all respondents) who endorsed multiple

positions, we assigned the highest-risk position based on mild TBI risk per 100 game positions.[44]

Body mass index during professional play was calculated using self-reported height and professional weight (<25.0, 25.0-30.0, or >30.0). Participants reported the number of seasons of professional play. For 70 men (2.1%) missing these data, total seasons were calculated using the first and last year of professional play or from Pro-Football Reference (PFR) data.[49] Participants were asked "During your active playing years, did you take any medications or other drugs to help performance?"

Participants were asked whether they had ever been recommended or prescribed medication for hypertension, high cholesterol levels, diabetes, heart failure, heart rhythm issues, and/or pain. They were separately asked if they had received a diagnosis of cancer, sleep apnea, or myocardial infarction or had undergone cardiac surgery. Participants were considered to have a heart condition if they reported heart rhythm issues, myocardial infarction, heart failure, or cardiac surgery. Self-reported weight and height were used to calculate their current BMI.

Anxious and depressive symptoms over the prior 2 weeks were assessed using the Patient Health Questionnaire 4. Responses were separately summed for anxious and depressive symptoms and dichotomized at more than 3 to indicate high depressive or anxiety symptoms.[50,51] Participants were considered to have depression or anxiety if they reported high symptoms or were currently prescribed antidepressants or anxiolytics, respectively. Alcohol intake was quantified as the total number of alcohol beverages consumed per week.

Statistical Analyses

We calculated the mean age, number of seasons, start year, and end year for study participants. To examine selection bias, we used PFR data to compare the FPHS cohort with all former players who played after 1960. Two-sample *t* tests and χ^2 tests were used to identify differences between the FPHS and PFR.

Concussion symptom frequency responses of none, once, 2 to 5 times, 6 to 10 times, or 11 or more were coded as 0, 1, 3.5, 8, and 13, respectively, and then summed to create a concussion symptom score. This score was then divided into quartiles to minimize the influence of outliers. Participants who did not respond to more than 5 concussion symptoms were excluded (n = 97). Of the 3409 remaining participants, 1 or more missing symptoms were imputed for 365 players (10.7%) via multiple imputation using chained equations.[52] Thirty-nine participants (1.1%) who did not respond to the LOC question were excluded from models examining LOC as the exposure. Data from participants who did not respond to outcome questions were excluded from related analyses (low testosterone levels, $N_{missing}$ = 75 [2.2%]; ED, $N_{missing}$ = 77 [2.3%]). Multiple imputation was used for covariates with missing data ($N_{missing}$ = 3 to 88).

To determine whether indicators of low testosterone levels and ED were more prevalent among men with established low testosterone levels and ED risk factors (eg, diabetes), we examined associations between risk factors and outcomes in age- and race-adjusted models. To measure the association of concussion symptom scores with indicators of low testosterone levels and ED, we calculated odds ratios (ORs) separately for indicators of low testosterone levels and ED as the dependent variable and concussion symptoms as the independent variable after adjusting for age and race. Models were further adjusted for football exposures and current health factors in exploratory analyses. To address the possibility that recall bias may have affected the number of reported concussion symptoms, we used LOC as a more easily recalled exposure.[53,54] To test for linear trends, the median of the concussion symptom quartile or LOC category was assigned to each participant and entered in models as a continuous variable. We additionally examined concussion scores and LOC as continuous measures. To determine whether current health factors statistically mediated associations between concussion scores and low testosterone levels or ED, we fit fully adjusted models with and without each current health factor. We calculated the percentage mediation for each variable as: $100*([\beta_{without\ mediator}-\beta_{with\ mediator}]/\beta_{without\ mediator})$.

To increase the likelihood that we were capturing men with low testosterone levels and ED, we separately considered only the subset of men who reported currently taking medication for low testosterone levels or ED as cases, excluding men who reported a history of medication recommendation or prescription but no current use. We next examined associations in younger players by restricting the data set to men 50 years or younger. We also restricted the data set to men who last played 20 years or fewer before the survey to determine whether concussion symptoms experienced 2 or more decades prior were associated with the outcomes. Depression and anxiety can lead to ED,[55-57] and low testosterone levels[58] and ED[59,60] may cause or exacerbate depression. We therefore included indicators of depression and anxiety in sensitivity analyses. To address the possibility that stigma associated with ED was associated with the response rate, we ran analyses in which all ED nonrespondents were imputed as either "no ED" or "have ED."

We used inverse probability weighting[61] to account for possible selection bias from nonparticipation in the FPHS. We predicted the probability of participation in the FPHS based on position, BMI, career length, and first and last year of professional play using PFR data. The inverse of these probabilities, stabilized and truncated at the 5th and 95th percentiles to minimize the effect of outliers, were used as weights in fully adjusted models of low testosterone levels and ED.[49,61] Odds ratios for all analyses were estimated using generalized linear models ("glm" package; R Statistical Software; R Foundation) and statistical significance was set at $P < .05$.

Results

Table 1 shows the distribution of demographic, football, and current health-related variables by concussion symptom quartile. Participants' mean (SD) age was 52.5 (14.1) years. Participants had played a mean (SD) of 6.8 (3.8) seasons. Respondents of the FPHS began their careers 4 years earlier than nonrespondents, ended their careers 3 years earlier, and had slightly longer careers (career start: t = 13.1; 95% CI, 3.2-4.4; career end: t = 9.3; 95% CI, 2.1-3.2; career duration: t = 14.3; 95% CI, −1.3 to −1.0; $P < .001$ for all). Playing position differed among respondents vs nonrespondents (offensive linemen:

Table 1. Demographic, Football, and Current Health Factors by Concussion Symptom Quartile for 3409 Participants

	Concussion Symptom Quartile, No. (%)			
Quartile (Concussion Score Range)	1 (0.0-10.5)	2 (10.5-23.0)	3 (23.5-43.5)	4 (43.5-130.0)
No.	853 (25.0)	852 (25.0)	852 (25.0)	852 (25.0)
Demographic Factors				
Age, y				
21-40	202 (23.7)	198 (23.2)	228 (26.8)	240 (28.2)
41-60	308 (36.1)	341 (40.0)	398 (46.7)	416 (48.8)
>60	343 (40.2)	313 (36.7)	226 (26.5)	196 (23.0)
Race/ethnicity				
Black	310 (36.6)	286 (34.2)	347 (41.2)	331 (39.1)
White	514 (60.8)	534 (63.9)	479 (56.8)	475 (56.1)
Other	22 (2.6)	16 (1.9)	17 (2.0)	40 (4.7)
Football Exposures				
BMI while playing professional football[a]				
<25.0	63 (7.4)	36 (4.2)	49 (5.8)	39 (4.6)
25.0-30.0	427 (50.1)	404 (47.4)	379 (44.5)	322 (37.8)
>30.0	363 (42.6)	412 (48.4)	423 (49.6)	491 (57.6)
Professional use of PED	87 (10.2)	99 (11.6)	135 (15.8)	229 (26.9)
Position				
Defensive back	117 (13.7)	118 (13.8)	142 (16.7)	122 (14.3)
Defensive line	104 (12.2)	83 (9.7)	82 (9.6)	100 (11.7)
Kicker/punter	61 (7.2)	23 (2.7)	14 (1.6)	6 (0.7)
Linebacker	81 (9.5)	79 (9.3)	86 (10.1)	113 (13.3)
Offensive line	137 (16.1)	179 (21.0)	155 (18.2)	157 (18.4)
Quarterback	51 (6.0)	58 (6.8)	36 (4.2)	18 (2.1)
Running back	70 (8.2)	68 (8.0)	87 (10.2)	94 (11.0)
Special teams only	3 (0.4)	10 (1.2)	8 (0.9)	6 (0.7)
Special speed	20 (2.3)	34 (4.0)	43 (5.0)	37 (4.3)
Special strength	36 (4.2)	49 (5.8)	48 (5.6)	56 (6.6)
Tight end	59 (6.9)	64 (7.5)	68 (8.0)	71 (8.3)
Wide receiver	114 (13.4)	87 (10.2)	83 (9.7)	72 (8.5)
Current health-related factors				
Hypertension	322 (37.7)	306 (35.9)	326 (38.3)	329 (38.6)
High cholesterol levels	272 (31.9)	289 (33.9)	309 (36.3)	303 (35.6)
Diabetes	60 (7.0)	92 (10.8)	76 (8.9)	72 (8.5)
Heart condition[b]	160 (18.8)	170 (20.0)	155 (18.2)	152 (17.8)
Prescription pain medication	127 (14.9)	203 (23.8)	280 (32.9)	360 (42.3)
Prostate or testicular cancer	33 (3.9)	42 (4.9)	24 (2.8)	33 (3.9)
Sleep apnea	127 (14.9)	178 (20.9)	198 (23.2)	257 (30.2)
Current BMI[a]				
<25.0	60 (7.0)	46 (5.4)	52 (6.1)	20 (2.3)
25.0-30.0	388 (45.5)	372 (43.7)	337 (39.6)	333 (39.1)
>30.0	401 (47.0)	429 (50.4)	457 (53.6)	494 (58.0)
Mood indicators				
Anxiety only	28 (3.3)	42 (4.9)	68 (8.0)	98 (11.5)
Depression only	17 (2.0)	30 (3.5)	47 (5.5)	45 (5.3)
Depression and anxiety	26 (3.0)	68 (8.0)	113 (13.3)	262 (30.8)
Alcohol drinks per wk				
None	268 (31.4)	270 (31.7)	253 (29.7)	271 (31.8)
1-7	314 (36.8)	329 (38.6)	309 (36.3)	314 (36.9)
8-14	158 (18.5)	146 (17.1)	145 (17.0)	137 (16.1)
≥15	99 (11.6)	101 (11.9)	134 (15.7)	122 (14.3)

Abbreviations: BMI, body mass index; PED, performance-enhancing drugs.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Heart condition includes self-reported heart rhythm issues, myocardial infarction, heart failure, or cardiac surgery.

Table 2. Prevalence of History of Low Testosterone Levels and Erectile Dysfunction Indicators by Demographic, Football, and Current Health Factors for 3409 Participants

Characteristic	No.	Prevalence of History of Prescription Recommendation by Self-report, No. (%)	
		Low Testosterone Levels	Erectile Dysfunction
All		611 (18.3)	755 (22.7)
Demographic Factors			
Age, y			
21-40	868	70 (8.2)	46 (5.4)
41-60	1463	301 (20.9)	307 (21.4)
>60	1078	240 (23.1)	402 (38.6)
Race			
Black	1274	210 (16.8)	280 (22.5)
White	2002	373 (19.1)	454 (23.2)
Other	95	23 (24.2)	14 (15.2)
Missing	38	5 (13.5)	7 (18.9)
Football Exposures			
BMI while playing professional football[a]			
<25.0	187	33 (17.7)	36 (19.9)
25.0-30.0	1532	243 (16.3)	353 (23.6)
>30.0	1689	334 (20.2)	365 (22.0)
Professional use of PED			
No	2859	471 (16.8)	608 (21.8)
Yes	550	140 (26.1)	147 (27.3)
Current Health-Related Factors			
Hypertension			
No	2083	287 (13.9)	297 (14.5)
Yes	1283	318 (25.5)	450 (35.9)
High cholesterol levels			
No	2165	292 (13.7)	352 (16.5)
Yes	1173	309 (27.0)	387 (33.6)
Diabetes			
No	3021	504 (16.9)	596 (20.0)
Yes	300	95 (32.5)	136 (46.7)
Heart condition[b]			
No	2772	437 (16.0)	522 (19.2)
Yes	637	174 (28.5)	233 (37.8)
Prescription pain medication			
No	2439	328 (13.7)	415 (17.4)
Yes	970	283 (29.9)	340 (35.7)
Prostate or testicular cancer			
No	3277	576 (18)	686 (21.4)
Yes	132	35 (27.1)	69 (54.3)
Sleep apnea			
No	2582	367 (14.5)	478 (18.8)
Yes	760	236 (31.9)	264 (35.7)
Current BMI[a]			
<25.0	178	16 (9.1)	32 (18.4)
25.0-30.0	1430	211 (15.1)	276 (19.8)
>30.0	1781	383 (22.0)	442 (25.4)
Mood indicators[c]			
No depression or anxiety	2562	357 (14.3)	479 (19.1)
Anxiety only	236	44 (19.0)	49 (21.2)
Depression only	139	36 (26.5)	43 (31.9)
Depression and anxiety	469	174 (37.8)	184 (40)
Alcohol drinks per wk			
None	1062	213 (20.5)	240 (23.1)
1-7	1266	210 (17.0)	266 (21.5)
8-14	586	97 (17.0)	128 (22.1)
≥15	456	85 (19.0)	111 (24.8)

Abbreviations: BMI, body mass index; PED, performance-enhancing drugs.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Heart condition includes self-reported heart rhythm issues, myocardial infarction, heart failure, or cardiac surgery.

[c] Derived from Patient Health Questionnaire 4.

FPHS, 21.7%; nonrespondents, 3.6%; $\chi^2 = 100.9$; $P < .001$; defensive backs: FPHS, 14.8%; nonrespondents, 9.9%; $\chi^2 = 40.7$; $P < .001$; running backs: FPHS, 9.4%; nonrespondents, 13.3%; $\chi^2 = 32.3$; $P < .001$; tight ends: FPHS, 7.7%; nonrespondents, 5.9%; $\chi^2 = 11.7$; $P < .001$; wide receivers: FPHS, 0.5%; nonrespondents, 12.4%; $\chi^2 = 7.9$; $P < .001$).

Of 3409 participants, 611 (18.3%) reported indicators of low testosterone levels, and 755 (22.7%) reported indicators of ED. Fewer than 10% of participants reported indicators of low testosterone levels and ED (335 [9.8%]). Of 611 players with low testosterone indicators, 243 (39.8%) were currently taking medication. Among players with indicators of ED, half were currently taking medication (379 [50.2%]). The prevalence of indicators of low testosterone levels and ED was greater in men with established risk factors (**Table 2**). In models that included age and race, indicators of low testosterone levels and ED were significantly associated with hypertension, high cholesterol levels, diabetes, heart conditions, prescription pain medication, reproductive cancer, sleep apnea, obesity, and mood disorders (**Table 3**).

We found statistically significant, monotonically increasing associations between concussion symptoms and indicators for low testosterone levels and ED in models adjusted for age and race (**Figure**; low testosterone OR, 3.49; 95% CI, 2.68-4.56; ED OR, 2.41; 95% CI, 1.87-3.11). In models further adjusted for professional football–related exposures (eg, position, BMI during professional play, and self-reported use of performance enhancing drugs), estimates remained essentially unchanged from age- and race-adjusted models (Figure; low testosterone OR, 3.38; 95% CI, 2.57-4.45; ED OR, 2.32; 95% CI, 1.78-3.02).

Associations in models further adjusted for current health factors were slightly attenuated but remained statistically significant (Figure; low testosterone OR, 2.39; 95% CI, 1.79-3.19;

ED OR, 1.72; 95% CI, 1.30-2.27). Loss of consciousness was associated with indicators of low testosterone levels and ED in models adjusted for demographics, football exposures, and current risk factors (Figure). In fully adjusted models with concussion symptoms and LOC coded as continuous variables, both were significantly associated with low testosterone levels and ED (concussion symptoms: low testosterone β = 1.01; 95% CI, 1.01-1.02; $P \leq .001$; ED β = 1.01; 95% CI, 1.01-1.01; $P \leq .001$; LOC: low testosterone β = 1.08; 95% CI, 1.04-1.12; $P \leq .001$; ED β = 1.06; 95% CI, 1.02-1.10; $P = .001$). For low testosterone, men with relatively low concussion scores (the second quartile) had significantly elevated ORs compared with men in the lowest quartile (OR, 1.41; 95% CI, 1.05-1.89; $P = .02$).

The largest statistical mediators of the association between concussion score and the outcomes were current use of prescription pain medication (low testosterone mediation, 7.9%; ED mediation, 20.4%) and sleep apnea (low testosterone mediation, 9.7%; ED mediation, 5.9%). All other current health factors statistically mediated the associations by less than 4%.

Results were similar in analyses restricted to participants currently using low testosterone and ED medication among players younger than 50 years, among players who played 20 years or longer before the study, and in inverse probability-weighted analyses. Further adjustment for mood indicators somewhat attenuated associations (**Table 4**). We conducted a post hoc analysis to compare associations among men with low testosterone levels only, ED only, and men with both. Associations with concussion symptoms were stronger among men reporting low testosterone levels and ED compared with men reporting only 1 of the 2 outcomes (eTable in the Supplement; highest concussion quartile vs lowest; men with low testosterone only: OR, 2.66; 95% CI, 1.84-3.83, $P < .001$; men with ED only: OR, 1.47; 95% CI, 1.06-2.04; $P = .02$; men with both outcomes: OR, 4.95; 95% CI, 3.40-7.22; $P < .001$).

Table 3. Low Testosterone Levels or ED Indicators in Association With Established Low Testosterone Levels and ED Risk Factors for 3409 Participants

Characteristic	Prevalence of History of Prescription Recommendation by Self-report, OR (95% CI)	
	Low Testosterone	ED
Model 1: Mutually Adjusted for Age and Race		
Age, y		
21-40	1 [Reference]	1 [Reference]
41-60	2.99 (2.27-3.94)[a]	4.82 (3.49-6.66)[a]
>60	3.41 (2.56-4.55)[a]	12.22 (8.79-16.98)[a]
Race/ethnicity		
White	1 [Reference]	1 [Reference]
Black	0.97 (0.80-1.17)	1.4 (1.17-1.69)[a]
Other	1.61 (0.98-2.64)	0.87 (0.47-1.59)
Missing	0.64 (0.25-1.67)	0.63 (0.27-1.50)
Models 2-10: Age and Race Adjusted		
Model 2: hypertension	1.81 (1.50-2.19)[a]	2.26 (1.89-2.71)[a]
Model 3: high cholesterol levels	1.96 (1.62-2.37)[a]	1.69 (1.41-2.02)[a]
Model 4: diabetes	2.04 (1.55-2.69)[a]	2.66 (2.04-3.45)[a]
Model 5: heart condition[b]	1.73 (1.39-2.15)[a]	1.64 (1.34-2.01)[a]
Model 6: prescription pain medication	2.53 (2.10-3.05)[a]	2.3 (1.93-2.75)[a]
Model 7: prostate or testicular cancer	1.31 (0.87-1.97)	2.54 (1.75-3.69)[a]
Model 8: sleep apnea	2.51 (2.07-3.05)[a]	2.04 (1.69-2.46)[a]
Model 9: current BMI[c]		
<25.0	1 [Reference]	1 [Reference]
25.0-30.0	1.93 (1.13-3.32)[d]	1.35 (0.88-2.06)
>30.0	3.11 (1.82-5.30)[a]	1.99 (1.31-3.02)[e]
Model 10: mood disorders		
None	1 [Reference]	1 [Reference]
Anxiety indicators only	1.63 (1.14-2.33)[e]	1.59 (1.12-2.26)[d]
Depression indicators only	2.22 (1.48-3.34)[a]	2.11 (1.41-3.15)[a]
Depression and anxiety indicators	4 (3.19-5.02)[a]	3.37 (2.67-4.24)[a]
Model 11: alcohol drinks per wk		
None	1 [Reference]	1 [Reference]
1-7	0.84 (0.68-1.05)	1.03 (0.84-1.27)
8-14	0.81 (0.61-1.06)	0.99 (0.76-1.28)
15+	0.94 (0.71-1.26)	1.27 (0.96-1.67)

Abbreviations: BMI, body mass index; ED, erectile dysfunction; OR, odds ratio.

[a] $P < .001$.

[b] Heart condition includes self-reported heart rhythm issues, myocardial infarction, heart failure, or cardiac surgery.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] $P < .05$.

[e] $P < .01$.

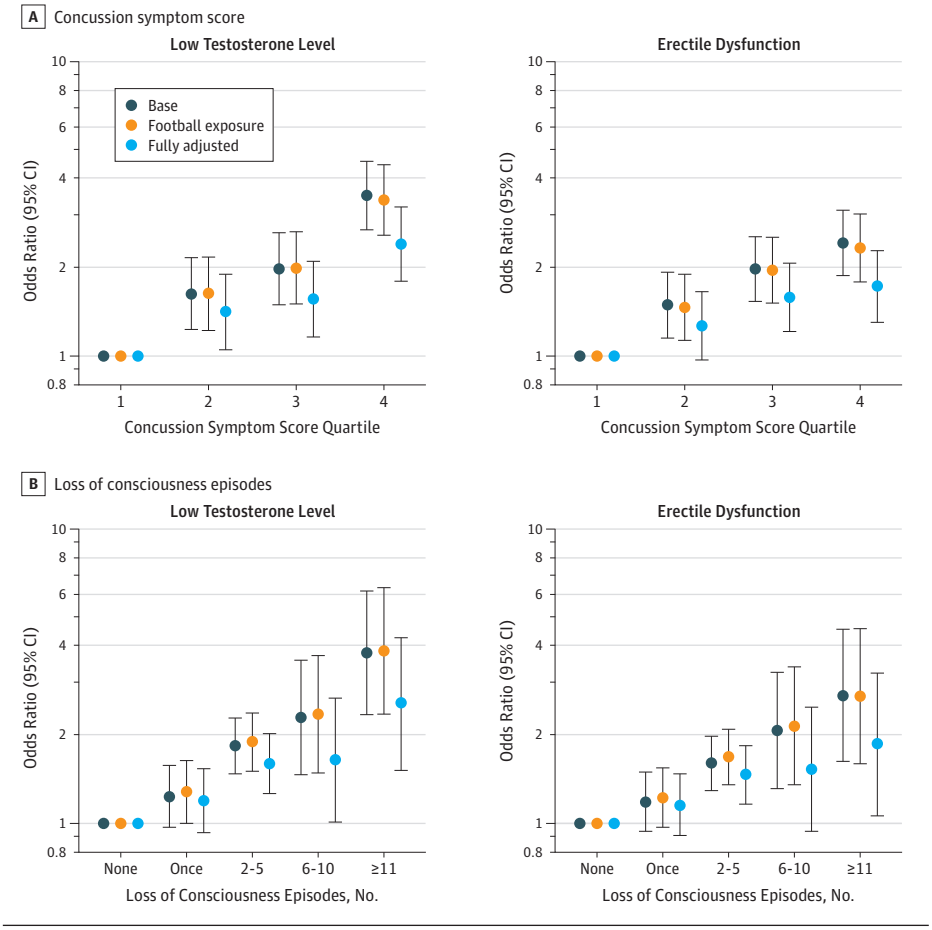
Discussion

We identified a highly robust, monotonically increasing association between self-reported concussion symptoms at the time of football injury and self-reported low testosterone levels and ED indicators. Even participants with relatively few concussion symptoms (ie, those in the second quartile) had significantly elevated odds of reporting low testosterone levels compared with men in the lowest quartile.

Our findings add to a literature composed of studies linking single head injuries with pituitary dysfunction in the general population,[6,9-11] small studies of professional boxers,[23-26,62,63] and findings from veterans with blast-induced head injury,[27-29] indicating that mechanical and blast-induced trauma may have associations with pituitary and sexual function. To our knowledge, this is the first large study to examine low testosterone levels and ED, albeit indirectly, in a nonclinical population with a high prevalence of repeated injuries. This is also the first study to adjust for risk factors such as BMI.

Several hypothesized mechanisms, including concussion-associated hypopituitarism, may explain the associations of concussion with low testosterone levels and ED. The pituitary gland is perfused by long portal vessels branching off the internal carotid artery,[64] making it susceptible to mechanical trauma, low cerebral blood flow, and increased intracranial pressure associated with head injury.[65,66] Acceleration and deceleration forces can shear axonal tracts that connect the pituitary to the hypothalamus. Thus, the combination of intracranial pressure, reduced blood flow, and diffuse axonal injury

Figure. Association Between Concussion Symptom Quartile and Loss of Consciousness With Low Testosterone and Erectile Dysfunction



A and B, The lowest quartile served as the reference for all models. The base model is adjusted for age and race/ethnicity; the football exposure model is further adjusted for body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) while playing professional football, position, and use of performance-enhancing drugs; and the fully adjusted model is further adjusted for current BMI, heart condition, diabetes, high cholesterol levels, hypertension, sleep apnea, use of prescription pain medication, alcohol drinks per week, and a history of testicular or prostate cancer. Linear tests of trend were significant ($P < .01$).

between the pituitary and the hypothalamus could cause diminished pituitary function, leading to low testosterone levels and ED. In exploratory mediation analyses, we found that adjusting for current prescription pain medication use and sleep apnea modestly attenuated the association of concussion symptoms with low testosterone levels and ED. These results suggest that pain medication and sleep apnea should be explored as possible pathways through which head injury affects hormone levels and sexual function.

Limitations

Our study has several limitations. First, we used indirect measures of low testosterone levels and ED. However, participant-reported health care clinician medication recommendations may be reasonable proxies: self-reported sexual dysfunction single-question assessments[67,68] have largely replaced invasive physiological tests in clinical and research settings.[69-71] Medical records, often a criterion standard for case ascertainment for other outcomes, may be less reliable for sexual dysfunction given that only 30% of men seek medical treatment for ED.[72] Nevertheless, US men are comparatively more likely to seek treatment vs men in European countries (56% vs 10%-47%) and more willing to take ED medication.[73] Moreover, the validity of our indicators is supported by statistically significant associations with known low testosterone and ED risk factors and by sensitivity analyses in men who self-reported currently using testosterone therapy and ED medication.

Second, concussion data were collected retrospectively, raising the possibility of recall bias. However, the robust monotonic association of the concussion exposure with the outcomes suggests simple recall bias may not solely account for our findings. Third, the concussion symptom scale has not been validated. To our knowledge, there is no validated retrospective measure of concussion symptoms. In our data, findings were similar using LOC count.[53,54,74,75] Moreover, simpler metrics, such as the number of diagnosed concussions, may not adequately capture the experience of concussion or concussion severity; at least 30% of concussions may be undiagnosed,[21,75,76] players may hide concussions,[21] and concussion management during professional play has changed over time.[45] Concussion symptoms have been used previously as a surrogate for head injury exposure and severity.[77-80]

Fourth, we do not know whether low testosterone levels or ED preceded men's exposure to professional football.

Table 4. Sensitivity Analyses for Low Testosterone Levels and Erectile Dysfunction Indicators for Each Quartile of Concussion Symptom Score for 3409 Participants

Model	No.		Concussion Symptom Quartile	History of Prescription Recommendation, OR (95%)	
	Low Testosterone Levels	Erectile Dysfunction		Low Testosterone Levels	Erectile Dysfunction
Model 1: base model[a]	3334	3332	1	1 [Reference]	1 [Reference]
			2	1.62 (1.23-2.15)[b]	1.49 (1.15-1.92)[b]
			3	1.97 (1.49-2.6)[c]	1.96 (1.53-2.53)[c]
			4	3.49 (2.68-4.56)[c]	2.41 (1.87-3.11)[c]
Model 2: case definition includes only current medication users[a]	3334	3332	1	1 [Reference]	1 [Reference]
			2	1.67 (1.10-2.56)[d]	1.21 (0.88-1.67)
			3	1.93 (1.26-2.94)[b]	1.65 (1.21-2.24)[b]
			4	3.02 (2.02-4.5)[c]	1.62 (1.18-2.24)[b]
Model 3: restricted to men ≤50 y[a]	1460	1457	1	1 [Reference]	1 [Reference]
			2	1.41 (0.84-2.38)	1.69 (0.90-3.18)
			3	1.72 (1.05-2.83)[d]	2.75 (1.53-4.93)[b]
			4	2.92 (1.83-4.66)[c]	3.29 (1.85-5.85)[c]
Model 4: men who last played ≥20 y prior[a]	1953	1953	1	1 [Reference]	1 [Reference]
			2	1.57 (1.14-2.17)[b]	1.48 (1.12-1.95)[b]
			3	1.76 (1.27-2.44)[b]	1.79 (1.35-2.38)[c]
			4	3.08 (2.24-4.24)[c]	2.09 (1.56-2.80)[c]
Model 5: fully adjusted including mood disorders[e]	3334	3332	1	1 [Reference]	1 [Reference]
			2	1.33 (0.99-1.78)	1.19 (0.91-1.56)
			3	1.41 (1.05-1. 90)[d]	1.43 (1.09-1.88)[d]
			4	1.89 (1.39-2.55)[c]	1.36 (1.02-1.83)[d]
Model 6: missing imputed as no[a]	3409	3409	1	1 [Reference]	1 [Reference]
			2	1.61 (1.22-2.13)[b]	1.48 (1.15-1.91)[b]
			3	1.91 (1.45-2.52)[c]	1.96 (1.52-2.52)[c]
			4	3.43 (2.63-4.48)[c]	2.34 (1.82-3.02)[c]
Model 7: missing imputed as yes[a]	3409	3409	1	1 [Reference]	1 [Reference]
			2	1.67 (1.29-2.17)[c]	1.51 (1.18-1.92)[b]
			3	2 (1.54-2.60)[c]	1.93 (1.52-2.46)[c]
			4	3.37 (2.61-4.34)[c]	2.46 (1.92-3.14)[c]
Model 8: inverse probability weighted[e]	3334	3332	1	1 [Reference]	1 [Reference]
			2	1.40 (1.04-1.89)[d]	1.34 (1.01-1.77)[d]
			3	1.50 (1.11-2.03)[b]	1.65 (1.25-2.19)[c]
			4	2.44 (1.82-3.29)[c]	1.90 (1.43-2.54)[c]

Abbreviation: OR, odds ratio.

[a] Adjusted for age and race.

[b] $P < .01$.

[c] $P < .001$.

[d] $P < .05$.

[e] Adjusted for age, race, professional body mass index (calculated as weight in kilograms divided by height in meters squared), position, use of performance-enhancing drugs, current body mass index, heart condition (eg, heart rhythm issues, myocardial infarction, heart failure, or cardiac surgery), diabetes, high cholesterol levels, hypertension, sleep apnea, alcohol beverages per week, use of prescription pain medication, and history of testicular or prostate cancer.

Fifth, the stigma surrounding sexual dysfunction could affect participants' likelihood of speaking to their health care clinician or responding honestly on the survey.[81] However, this would only produce the results presented in this article if such under-reporting were less likely among men with more reported concussion symptoms. Sixth, bias from the relatively low participation rate could have affected our estimates,[82] although statistically significant monotonic relationships persisted in inverse probability of participation-weighted analyses. Seventh, illicit drug use may affect low testosterone[83,84] and ED[85]; however, we did not query illicit drug use. Finally, health status may have been associated with players' decisions to participate: the healthiest players may have been less motivated to participate and the players with the most impairment may have been unable to participate.[82] However, measures of association would be biased only if participation was concurrently associated with the exposure (concussion symptoms) and the outcome (low testosterone levels or ED).[86]

Conclusions

This study's data suggest that concussion symptoms experienced during playing years may place NFL players at risk of low testosterone levels and ED decades later. These findings have implications for civilians and veterans who have experienced head injury, as well as for participants in combative and contact sports (eg, mixed martial arts, hockey, boxing, and soccer) who may experience repeated head trauma. Replication of our findings among nonprofessional football players and in the general population is a critical next step. Treatments for testosterone insufficiency and ED, including testosterone replacement therapy and phosphodiesterase type 5 inhibitors,

are generally considered safe and have high efficacy rates.[87-89] Our results could encourage clinicians to proactively query these treatable outcomes in patients with brain injuries as well as motivate future longitudinal studies to increase our understanding of the causal association between concussion and low testosterone levels and ED.

ARTICLE INFORMATION

Accepted for Publication: June 21, 2019.

Published Online: August 26, 2019. doi:10.1001/jamaneurol.2019.2664

Author Affiliations: Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Grashow, Weisskopf, Speizer, Courtney, Roberts); Football Players Health Study, Harvard Medical School, Boston, Massachusetts (Grashow, Weisskopf, Miller, Nathan, Zafonte, Speizer, Courtney, Baggish, Taylor, Pascual-Leone, Nadler); Environmental and Occupational Medicine and Epidemiology Program, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Weisskopf, Courtney); Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital, Boston (Miller); Harvard Medical School, Boston, Massachusetts (Miller); Massachusetts General Hospital Diabetes Center, Boston (Nathan); Department of Medicine, Harvard Medical School, Boston, Massachusetts (Nathan); Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Boston, Massachusetts (Zafonte); Massachusetts General Hospital, Harvard Medical School, Boston (Zafonte); Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Zafonte); Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Speizer); Cardiovascular Performance Program, Massachusetts General Hospital, Boston (Baggish); Cardiovascular Research Institute, Morehouse School of Medicine, Atlanta, Georgia (Taylor); Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (Pascual-Leone); Dana Farber Cancer Institute, Boston, Massachusetts (Nadler).

Author Contributions: Dr Grashow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Grashow, Weisskopf, Miller, Nathan, Zafonte, Speizer, Pascal-Leone, Roberts.
Acquisition, analysis, or interpretation of data: Grashow, Weisskopf, Miller, Zafonte, Speizer, Courtney, Baggish, Taylor, Pascal-Leone, Nadler, Roberts.
Drafting of the manuscript: Grashow, Miller, Zafonte, Baggish, Roberts.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Grashow, Weisskopf, Roberts.
Obtained funding: Zafonte, Courtney, Taylor, Pascal-Leone.
Administrative, technical, or material support: Grashow, Nathan, Courtney, Taylor, Pascal-Leone.
Supervision: Weisskopf, Miller, Nathan, Zafonte, Baggish, Pascal-Leone, Nadler, Roberts.
Other - design of data collection instruments and supervision of data acquisition: Speizer.

Conflict of Interest Disclosures: Drs Grashow, Miller, and Roberts reported grants from the NFL Players Association (NFLPA) during the conduct of the study. Dr Weisskopf reported grants from the NFLPA during the conduct of the study and personal fees from Partners Health Care. Dr Zafonte reported receiving royalties from Oakstone and Demos (serving as coeditor of the text *Brain Injury Medicine*) and serves on the scientific advisory boards of Oxeia Biopharma, Biodirection, ElMINDA, and Myomo. He was partially supported by grants from the National Institute on Disability, Independent Living, and Rehabilitation Research (90DP0039-03-00, 90SI5007-02-04, 90DP0060); US Army Medical Research & Development Command (W81XWH-112-0210); the National Institutes of Health (4 U01NS086090-04, 5R24HD082302-02, and 5U01NS091951-03), and the Football Players Health Study at Harvard University, which is funded by the NFLPA. Dr Zafonte also evaluates patients for the MGH Brain and Body TRUST center sponsored in part by the NFLPA and serves on the Mackey White health committee. Dr Courtney reported grant support from the NFLPA and the Football Players Health Study at Harvard University, which was in turn sponsored by the NFLPA during the development, submission and revision of the manuscript. Dr Baggish reported receiving funding from the National Institutes of Health/National Heart, Lung, and Blood Institute, the NFLPA, the American Heart Association, the American Society of Echocardiography, and the US Department of Defense. He serves as an associate editor for *Medicine Science in Sports & Exercise* and is on the editorial board for *Circulation*. He receives compensation for his role as team cardiologist from US Soccer, US Rowing, the New England Patriots, the Boston Bruins, the New England Revolution, and Harvard University. Dr Pascal-Leone reported personal fees from Neosync, Neuroelectrics, Starlab, Constant Therapy, and Cognito outside the submitted work. He serves as associate editor for *Annals of Neurology*. No other disclosures were reported.

Funding/Support: This study was partly supported by the Sidney R. Baer Jr Foundation, the National Institutes of Health (grants R01MH100186, R21AG051846, R01MH111875, R01MH115949, R01 MH117063, R24AG06142, and P01 AG031720), the National Science Foundation, DARPA, the Football Players Health Study at Harvard University, and Harvard Catalyst/The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Studies National Institutes of Health grant UL1 RR025758; Dr Pascual Leone) as well as the NFLPA.

Role of the Funder/Sponsor: The NFLPA had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: All of the information and materials in this manuscript are original.

Additional Contributions: We thank the study participants, advisors, and staff of the Football Players Health Study. The staff received compensation for their contributions.

REFERENCES

1. McCabe MP, Althof SE. A systematic review of the psychosocial outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man's inability to have sex? *J Sex Med*. 2014;11(2):347-363. doi:10.1111/jsm.12374

2. Rowland DL. Psychological impact of premature ejaculation and barriers to its recognition and treatment. *Curr Med Res Opin*. 2011;27(8):1509-1518. doi:10.1185/03007995.2011.590968

3. Carroll JL, Bagley DH. Evaluation of sexual satisfaction in partners of men experiencing erectile failure. *J Sex Marital Ther*. 1990;16(2):70-78. doi:10.1080/00926239008405253

4. McCabe MP. Relationship factors in the development and maintenance of ED: implications for treatment effectiveness. *J Sex Med*. 2008;5(8):1795-1804. doi:10.1111/j.1743-6109.2008.00878.x

5. Montorsi F, Adaikan G, Becher E, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med*. 2010;7(11):3572-3588. doi:10.1111/j.1743-6109.2010.02062.x

6. Yang YJ, Chien WC, Chung CH, et al. Risk of erectile dysfunction after traumatic brain injury: a nationwide population-based cohort study in Taiwan. *Am J Mens Health*. 2018;12(4):913-925. doi:10.1177/1557988317750970

7. Klose M, Jonsson B, Abs R, et al. From isolated GH deficiency to multiple pituitary hormone deficiency: an evolving continuum—a KIMS analysis. *Eur J Endocrinol*. 2009;161(suppl 1):S75-S83. doi:10.1530/EJE-09-0328

8. Scranton RA, Baskin DS. Impaired pituitary axes following traumatic brain injury. *J Clin Med*. 2015;4(7):1463-1479. doi:10.3390/jcm4071463

9. Simpson GK, McCann B, Lowy M. Treating male sexual dysfunction after traumatic brain injury: two case reports. *NeuroRehabilitation*. 2016;38(3):281-289. doi:10.3233/NRE-161319

10. Hibbard MR, Gordon WA, Flanagan S, Haddad L, Labinsky E. Sexual dysfunction after traumatic brain injury. *NeuroRehabilitation*. 2000;15(2):107-120.

11. Sander AM, Maestas KL, Nick TG, et al. Predictors of sexual functioning and satisfaction 1 year following traumatic brain injury: a TBI model systems multicenter study. *J Head Trauma Rehabil*. 2013;28(3):186-194. doi:10.1097/HTR.0b013e31828b4f91

12. Ponsford J. Sexual changes associated with traumatic brain injury. *Neuropsychol Rehabil*. 2003;13(1-2):275-289. doi:10.1080/09602010244000363

13. Kreuter M, Dahllöf AG, Gudjonsson G, Sullivan M, Siösteen A. Sexual adjustment and its predictors after traumatic brain injury. *Brain Inj*. 1998;12(5):349-368. doi:10.1080/026990598122494

14. Kreutzer JS, Zasler ND. Psychosexual consequences of traumatic brain injury: methodology and preliminary findings. *Brain Inj*. 1989;3(2):177-186. doi:10.3109/02699058909004550

15. Kosteljanetz M, Jensen TS, Nørgård B, Lunde I, Jensen PB, Johnsen SG. Sexual and hypothalamic dysfunction in the postconcussional syndrome. *Acta Neurol Scand*. 1981;63(3):169-180. doi:10.1111/j.1600-0404.1981.tb00769.x

16. Downing MG, Stolwyk R, Ponsford JL. Sexual changes in individuals with traumatic brain injury: a control comparison. *J Head Trauma Rehabil*. 2013;28(3):171-178. doi:10.1097/HTR.0b013e31828b4f63

17. War FA, Jamuna R, Arivazhagan A. Cognitive and sexual functions in patients with traumatic brain injury. *Asian J Neurosurg*. 2014;9(1):29-32. doi:10.4103/1793-5482.131061

18. Sander AM, Maestas KL, Pappadis MR, Sherer M, Hammond FM, Hanks R; NIDRR Traumatic Brain Injury Model Systems Module Project on Sexuality After TBI. Sexual functioning 1 year after traumatic brain injury: findings from a prospective traumatic brain injury model systems collaborative study. *Arch Phys Med Rehabil*. 2012;93(8):1331-1337. doi:10.1016/j.apmr.2012.03.037

19. Sandel ME, Williams KS, Dellapietra L, Derogatis LR. Sexual functioning following traumatic brain injury. *Brain Inj*. 1996;10(10):719-728. doi:10.1080/026990596123981

20. Hobbs JG, Young JS, Bailes JE. Sports-related concussions: diagnosis, complications, and current management strategies. *Neurosurg Focus*. 2016;40(4):E5. doi:10.3171/2016.1.FOCUS15617

21. Kerr ZY, Mihalik JP, Guskiewicz KM, Rosamond WD, Evenson KR, Marshall SW. Agreement between athlete-recalled and clinically documented concussion histories in former collegiate athletes. *Am J Sports Med*. 2015;43(3):606-613. doi:10.1177/0363546514562180

22. Silva PP, Bhatnagar S, Herman SD, et al. Predictors of hypopituitarism in patients with traumatic brain injury. *J Neurotrauma*. 2015;32(22):1789-1795. doi:10.1089/neu.2015.3998

23. Tanriverdi F, Unluhizarci K, Kocyigit I, et al. Brief communication: pituitary volume and function in competing and retired male boxers. *Ann Intern Med*. 2008;148(11):827-831. doi:10.7326/0003-4819-148-11-200806030-00005

24. Kelestimur F, Tanriverdi F, Atmaca H, Unluhizarci K, Selcuklu A, Casanueva FF. Boxing as a sport activity associated with isolated GH deficiency. *J Endocrinol Invest*. 2004;27(11):RC28-RC32. doi:10.1007/BF03345299

25. Tanriverdi F, De Bellis A, Battaglia M, et al. Investigation of antihypothalamus and antipituitary antibodies in amateur boxers: is chronic repetitive head trauma-induced pituitary dysfunction associated with autoimmunity? *Eur J Endocrinol*. 2010;162(5):861-867. doi:10.1530/EJE-09-1024

26. Kelly DF, Chaloner C, Evans D, et al. Prevalence of pituitary hormone dysfunction, metabolic syndrome, and impaired quality of life in retired professional football players: a prospective study. *J Neurotrauma*. 2014;31(13):1161-1171. doi:10.1089/neu.2013.3212

27. Wilkinson CW, Pagulayan KF, Petrie EC, et al. High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. *Front Neurol*. 2012;3:11. doi:10.3389/fneur.2012.00011

28. Baxter D, Sharp DJ, Feeney C, et al. Pituitary dysfunction after blast traumatic brain injury: the UK BIOSAP study. *Ann Neurol*. 2013;74(4):527-536. doi:10.1002/ana.23958

29. Undurti A, Colasurdo EA, Sikkema CL, et al. Chronic hypopituitarism associated with increased postconcussive symptoms is prevalent after blast-induced mild traumatic brain injury. *Front Neurol*. 2018;9:72. doi:10.3389/fneur.2018.00072

30. Albuquerque FN, Kuniyoshi FH, Calvin AD, et al. Sleep-disordered breathing, hypertension, and obesity in retired National Football League players. *J Am Coll Cardiol*. 2010;56(17):1432-1433. doi:10.1016/j.jacc.2010.03.099

31. Luyster FS, Dunn RE, Lauderdale DS, et al. Sleep-apnea risk and subclinical atherosclerosis in early-middle-aged retired National Football League players. *Nat Sci Sleep*. 2017;9:31-38. doi:10.2147/NSS.S125228

32. Baron SL, Hein MJ, Lehman E, Gersic CM. Body mass index, playing position, race, and the cardiovascular mortality of retired professional football players. *Am J Cardiol*. 2012;109(6):889-896. doi:10.1016/j.amjcard.2011.10.050

33. Tucker AM, Vogel RA, Lincoln AE, et al. Prevalence of cardiovascular disease risk factors among National Football League players. *JAMA*. 2009;301(20):2111-2119. doi:10.1001/jama.2009.716

34. Trexler ET, Smith-Ryan AE, Defreese JD, Marshall SW, Guskiewicz KM, Kerr ZY. Associations between BMI change and cardiometabolic risk in retired football players. *Med Sci Sports Exerc*. 2018;50(4):684-690. doi:10.1249/MSS.0000000000001492

35. Cottler LB, Ben Abdallah A, Cummings SM, Barr J, Banks R, Forchheimer R. Injury, pain, and prescription opioid use among former National Football League (NFL) players. *Drug Alcohol Depend*. 2011;116(1-3):188-194. doi:10.1016/j.drugalcdep.2010.12.003

36. Guskiewicz KM, Marshall SW, Bailes J, et al. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*. 2007;39(6):903-909. doi:10.1249/mss.0b013e3180383da5

37. Schwenk TL, Gorenflo DW, Dopp RR, Hipple E. Depression and pain in retired professional football players. *Med Sci Sports Exerc*. 2007;39(4):599-605. doi:10.1249/mss.0b013e31802fa679

38. Webner D, Iverson GL. Suicide in professional American football players in the past 95 years. *Brain Inj*. 2016;30(13-14):1718-1721. doi:10.1080/02699052.2016.1202451

39. Allen TW, Vogel RA, Lincoln AE, Dunn RE, Tucker AM. Body size, body composition, and cardiovascular disease risk factors in NFL players. *Phys Sportsmed*. 2010;38(1):21-27. doi:10.3810/psm.2010.04.1758

40. Camilo J, Helzberg JH. Obesity and metabolic syndrome in football players. *Can J Diabetes*. 2011;35(5):486-487. doi:10.1016/S1499-2671(11)80002-X

41. Churchill TW, Krishnan S, Weisskopf M, et al. Weight gain and health affliction among former National Football League players. *Am J Med*. 2018;131(12):1491-1498. doi:10.1016/j.amjmed.2018.07.042

42. Horn S, Gregory P, Guskiewicz KM. Self-reported anabolic-androgenic steroids use and musculoskeletal injuries: findings from the center for the study of retired athletes health survey of retired NFL players. *Am J Phys Med Rehabil*. 2009;88(3):192-200. doi:10.1097/PHM.0b013e318198b622

43. Zafonte R, Pascual-Leone A, Baggish A, et al. The Football Players' Health Study at Harvard University: design and objectives. *Am J Ind Med*. 2019;62(8):643-654. doi:10.1002/ajim.22991

44. Pellman EJ, Powell JW, Viano DC, et al. Concussion in professional football: epidemiological features of game injuries and review of the literature--part 3. *Neurosurgery*. 2004;54(1):81-94. doi:10.1227/01.NEU.0000097267.54786.54

45. Casson IR, Viano DC, Powell JW, Pellman EJ. Twelve years of national football league concussion data. *Sports Health*. 2010;2(6):471-483. doi:10.1177/1941738110383963

46. Chambers CC, Lynch TS, Gibbs DB, et al. Superior labrum anterior-posterior tears in the National Football League. *Am J Sports Med*. 2017;45(1):167-172. doi:10.1177/0363546516673350

47. Dodson CC, Secrist ES, Bhat SB, Woods DP, Deluca PF. Anterior cruciate ligament injuries in National Football League athletes from 2010 to 2013: a descriptive epidemiology study. *Orthop J Sports Med*. 2016;4(3):2325967116631949. doi:10.1177/2325967116631949

48. Lehman EJ. Epidemiology of neurodegeneration in American-style professional football players. *Alzheimers Res Ther*. 2013;5(4):34. doi:10.1186/alzrt188

49. Pro-Football-Reference. Sports reference. https://www.pro-football-reference.com/. Accessed August 15, 2014.

50. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry*. 2016;39:24-31. doi:10.1016/j.genhosppsych.2015.11.005

51. Kroenke K, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics*. 2009;50(6):613-621.

52. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393

53. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75(9):1055-1061. doi:10.1001/jamaneurol.2018.0815

54. Luis CA, Vanderploeg RD, Curtiss G. Predictors of postconcussion symptom complex in community dwelling male veterans. *J Int Neuropsychol Soc*. 2003;9(7):1001-1015. doi:10.1017/S1355617703970044

55. Singh R, Mason S, Lecky F, Dawson J. Prevalence of depression after TBI in a prospective cohort: the SHEFBIT study. *Brain Inj*. 2018;32(1):84-90. doi:10.1080/02699052.2017.1376756

56. Broshek DK, De Marco AP, Freeman JR. A review of post-concussion syndrome and psychological factors associated with concussion.

Brain Inj. 2015;29(2):228-237. doi:10.3109/02699052.2014.974674

57. Fann JR, Burington B, Leonetti A, Jaffe K, Katon WJ, Thompson RS. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. *Arch Gen Psychiatry*. 2004;61(1):53-61. doi:10.1001/archpsyc.61.1.53

58. Westley CJ, Amdur RL, Irwig MS. High rates of depression and depressive symptoms among men referred for borderline testosterone levels. *J Sex Med*. 2015;12(8):1753-1760. doi:10.1111/jsm.12937

59. Shiri R, Koskimäki J, Tammela TL, Häkkinen J, Auvinen A, Hakama M. Bidirectional relationship between depression and erectile dysfunction. *J Urol*. 2007;177(2):669-673. doi:10.1016/j.juro.2006.09.030

60. Seidman SN, Roose SP. The relationship between depression and erectile dysfunction. *Curr Psychiatry Rep*. 2000;2(3):201-205. doi:10.1007/s11920-996-0008-0

61. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164

62. Tanriverdi F, De Bellis A, Bizzarro A, et al. Antipituitary antibodies after traumatic brain injury: is head trauma-induced pituitary dysfunction associated with autoimmunity? *Eur J Endocrinol*. 2008;159(1):7-13. doi:10.1530/EJE-08-0050

63. Tanriverdi F, Unluhizarci K, Karaca Z, Casanueva FF, Kelestimur F. Hypopituitarism due to sports related head trauma and the effects of growth hormone replacement in retired amateur boxers. *Pituitary*. 2010;13(2):111-114. doi:10.1007/s11102-009-0204-0

64. Hohl A, Mazzuco TL, Coral MH, Schwarzbold M, Walz R. Hypogonadism after traumatic brain injury. *Arq Bras Endocrinol Metabol*. 2009;53(8):908-914. doi:10.1590/S0004-27302009000800003

65. Sundaram NK, Geer EB, Greenwald BD. The impact of traumatic brain injury on pituitary function. *Endocrinol Metab Clin North Am*. 2013;42(3):565-583. doi:10.1016/j.ecl.2013.05.003

66. Tanriverdi F, Schneider HJ, Aimaretti G, Masel BE, Casanueva FF, Kelestimur F. Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. *Endocr Rev*. 2015;36(3):305-342. doi:10.1210/er.2014-1065

67. O'Donnell AB, Araujo AB, Goldstein I, McKinlay JB. The validity of a single-question self-report of erectile dysfunction: results from the Massachusetts Male Aging Study. *J Gen Intern Med*. 2005;20(6):515-519. doi:10.1111/j.1525-1497.2005.0076.x

68. Derby CA, Araujo AB, Johannes CB, Feldman HA, McKinlay JB. Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. *Int J Impot Res*. 2000;12(4):197-204. doi:10.1038/sj.ijir.3900542

69. Lehmann K, Eichlisberger R, Gasser TC. Lack of diagnostic tools to prove erectile dysfunction: consequences for reimbursement? *J Urol*. 2000;163(1):91-94. doi:10.1016/S0022-5347(05)67980-3

70. Conte HR. Development and use of self-report techniques for assessing sexual functioning: a review and critique. *Arch Sex Behav*. 1983;12(6):555-576. doi:10.1007/BF01542217

71. Cappelleri JC, Siegel RL, Glasser DB, Osterloh IH, Rosen RC. Relationship between patient self-assessment of erectile dysfunction and the sexual health inventory for men. *Clin Ther*. 2001;23(10):1707-1719. doi:10.1016/S0149-2918(01)80138-7

72. Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. *Int J Impot Res*. 2003;15(1):63-71. doi:10.1038/sj.ijir.3900949

73. Shabsigh R, Perelman MA, Laumann EO, Lockhart DC. Drivers and barriers to seeking treatment for erectile dysfunction: a comparison of six countries. *BJU Int*. 2004;94(7):1055-1065. doi:10.1111/j.1464-410X.2004.05104.x

74. Didehbani N, Wilmoth K, Fields L, et al. Reliability of self-reported concussion history in retired NFL players. *Annals of Sports Medicine and Research*. 2017;4(3):1115. https://www.researchgate.net/publication/326020485_Reliability_of_Self-Reported_Concussion_History_in_Retired_NFL_Players. Accessed January 16, 2018.

75. Meehan WP III, Mannix RC, O'Brien MJ, Collins MW. The prevalence of undiagnosed concussions in athletes. *Clin J Sport Med*. 2013;23(5):339-342. doi:10.1097/JSM.0b013e318291d3b3

76. LaBotz M, Martin MR, Kimura IF, Hetzler RK, Nichols AW. A comparison of a preparticipation evaluation history form and a symptom-based concussion survey in the identification of previous head injury in collegiate athletes. *Clin J Sport Med*. 2005;15(2):73-78. doi:10.1097/01.jsm.0000157649.99867.fc

77. Chen JK, Johnston KM, Collie A, McCrory P, Ptito A. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry*. 2007;78(11):1231-1238. doi:10.1136/jnnp.2006.110395

78. Randolph C, Millis S, Barr WB, et al. Concussion symptom inventory: an empirically derived scale for monitoring resolution of symptoms following sport-related concussion. *Arch Clin Neuropsychol*. 2009;24(3):219-229. doi:10.1093/arclin/acp025

79. Henry LC, Tremblay S, Boulanger Y, Ellemberg D, Lassonde M. Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *J Neurotrauma*. 2010;27(1):65-76. doi:10.1089/neu.2009.0962

80. Erlanger D, Kaushik T, Cantu R, et al. Symptom-based assessment of the severity of a concussion. *J Neurosurg*. 2003;98(3):477-484. doi:10.3171/jns.2003.98.3.0477

81. Sotomayor M. The burden of premature ejaculation: the patient's perspective. *J Sex Med*. 2005;2(suppl 2):110-114. doi:10.1111/j.1743-6109.2005.20371.x

82. Grashow RG, Roberts AL, Zafonte R, et al. Defining exposures in professional football: professional American-style football players as an occupational cohort. *Orthop J Sports Med*. 2019;7(2):2325967119829212. doi:10.1177/2325967119829212

83. Brown TT, Wisniewski AB, Dobs AS. Gonadal and adrenal abnormalities in drug users: cause or consequence of drug use behavior and poor health outcomes. *Am J Infect Dis*. 2006;2(3):130-135. doi:10.3844/ajidsp.2006.130.135

84. Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. *J Androl*. 2012;33(4):515-528. doi:10.2164/jandrol.110.011874

85. Johnson SD, Phelps DL, Cottler LB. The association of sexual dysfunction and substance use among a community epidemiological sample. *Arch Sex Behav*. 2004;33(1):55-63. doi:10.1023/B:ASEB.0000007462.97961.5a

86. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615-625. doi:10.1097/01.ede.0000135174.63482.43

87. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. *Eur Urol*. 2013;63(5):902-912. doi:10.1016/j.eururo.2013.01.012

88. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? *Drugs*. 2005;65(12):1621-1650. doi:10.2165/00003495-200565120-00003

89. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag*. 2009;5(3):427-448.

1. Carson CC 3rd. Efficacy of antibiotic impregnation of inflatable penile prostheses in decreasing infection in original implants. *J Urol*. 2004 Apr. 171(4):1611-4. [Medline].
2. Massey FJ Jr, Bernstein GS, O'Fallon WM, Schuman LM, Coulson AH, Crozier R, et al. Vasectomy and health. Results from a large cohort study. *JAMA*. 1984 Aug 24-31. 252(8):1023-9. [Medline].
3. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*. 1994 Jan. 151(1):54-61. [Medline].
4. Rosenberg MT, Adams PL, McBride TA, Roberts JN, McCallum SW. Improvement in duration of erection following phosphodiesterase type 5 inhibitor therapy with vardenafil in men with erectile dysfunction: the ENDURANCE study. *Int J Clin Pract*. 2009 Jan. 63(1):27-34. [Medline]. [Full Text].
5. Cilurzo P, Canale D, Turchi P, Giorgi PM, Menchini Fabris GF. [The Rigiscan system in the diagnosis of male sexual impotence]. *Arch Ital Urol Nefrol Androl*. 1992 Jun. 64 Suppl 2:81-5. [Medline].
6. de Groat WC, Steers WD. Neuroanatomy and neurophysiology of penile erection. Tanagho E, Lue TF, McClure RD, eds. *Contemporary Management of Impotence and Infertility*. Baltimore, Md: Williams & Wilkins; 1988. 3-27.
7. Hedlund H, Andersson KE. Comparison of the responses to drugs acting on adrenoreceptors and muscarinic receptors in human isolated corpus cavernosum and cavernous artery. *J Auton Pharmacol*. 1985 Mar. 5(1):81-8. [Medline].
8. Diederichs W, Stief CG, Lue TF, Tanagho EA. Norepinephrine involvement in penile detumescence. *J Urol*. 1990 Jun. 143(6):1264-6. [Medline].
9. Ignarro LJ, Bush PA, Buga GM, Wood KS, Fukuto JM, Rajfer J. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. *Biochem Biophys Res Commun*. 1990 Jul 31. 170(2):843-50. [Medline].
10. Kim N, Azadzoi KM, Goldstein I, Saenz de Tejada I. A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. *J Clin Invest*. 1991 Jul. 88(1):112-8. [Medline]. [Full Text].
11. Holmquist F, Stief CG, Jonas U, Andersson KE. Effects of the nitric oxide synthase inhibitor NG-nitro-L-arginine on the erectile response to cavernous nerve stimulation in the rabbit. *Acta Physiol Scand*. 1991 Nov. 143(3):299-304. [Medline].
12.

Sexual Medicine Reviews
Volume 7, Issue 3, July 2019, Pages 464-475

Review

Testosterone Replacement Therapy for Sexual Symptoms

Giulia Rastrelli MD, PhD [1], Federica Guaraldi MD [2, 3], Yacov Reismann MD [4], Alessandra Sforza MD [3], Andrea M. Isidori MD [5], Mario Maggi MD [1], Giovanni Corona MD, PhD [3]

https://doi.org/10.1016/j.sxmr.2018.11.005

Abstract

Background

Several data have clearly shown that the endocrine system—and androgens in particular—play a pivotal role in regulating all the steps involved in the male sexual response cycle. Accordingly, testosterone (T) replacement therapy (TRT) represents a cornerstone of pharmacologic management of hypogonadal subjects with erectile dysfunction.

Aim

The aim of this review is to summarize all the available evidence supporting the role of T in the regulation of male sexual function and to provide a comprehensive summary regarding the sexual outcomes of TRT in patients complaining of sexual dysfunction.

Methods

A comprehensive PubMed literature search was performed.

Main Outcome Measure

Specific analysis of preclinical and clinical evidence on the role of T in regulating male sexual function was performed. In addition, available evidence supporting the role of TRT on several sexual outcomes was separately investigated.

Results

T represents an important modulator of male sexual response function. However, the role of T in sexual functioning is less evident in epidemiologic studies because other factors, including organic, relational, and intrapsychic determinants, can orchestrate their effect independently from the state of androgens. Nonetheless, it is clear that TRT can ameliorate several aspects of sexual functioning, including libido, erectile function, and overall sexual satisfaction. Conversely, data on the role of TRT in improving orgasmic function are more conflicting. Finally, further controlled studies are needed to investigate the combination of TRT and PDE5 inhibitors.

Conclusion

Positive effects of TRT are observed only in the presence of a hypogonadal status (ie, total T < 12 nmol/L). In addition, TRT alone can be effective in restoring only milder forms of erectile dysfunction, whereas the combined therapy with other drugs is required when more severe vascular damage is present.

Rastrelli G, Guaraldi F, Reismann Y, et al. Testosterone Replacement Therapy for Sexual Symptoms. Sex Med Rev 2019;7:464–475.

Previous Next

Key Words

Testosterone; Testosterone Replacement Therapy; Sexual Desire; Erectile Dysfunction; Ejaculation

Recommended articles Citing articles (18)

Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

View full text

DIABETIC Medicine

DiABETES UK
KNOW DIABETES. FIGHT DIABETES.

Systematic Review or Meta-analysis

Testosterone therapy for sexual dysfunction in men with Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

M. Algeffari,C. N. Jayasena,P. MacKeith,A. Thapar,W. S. Dhillo,N. Oliver

First published: 24 November 2017
https://doi.org/10.1111/dme.13553
Citations: 14

M.A. and C.N.J. are joint first authors.

Abstract

Aim

To evaluate the effectiveness of testosterone therapy on a range of sexual function domains in men with Type 2 diabetes.

Method

Electronic databases were searched for studies investigating the effect of testosterone therapy on sexual function in men with Type 2 diabetes. All randomized controlled trials were considered for inclusion if they compared the efficacy of testosterone therapy with that of placebo and reported sexual function outcomes. Statistical analysis was performed using a random-effects model, and heterogeneity was expressed using the I^2 statistic.

Results

A total of 611 articles were screened. Six randomized control trials, in a total of 587 men with Type 2 diabetes, were eligible for inclusion. The pooled data suggested that testosterone therapy improves sexual desire (random-effects pooled effect size 0.314; 95% CI 0.082–0.546) and erectile function (random-effects pooled effect size 0.203; 95% CI 0.007–0.399) when compared with control groups. Testosterone therapy had no significant effect on constitutional symptoms or other sexual domains compared with control groups. No studies have investigated the incidence of prostate cancer, fertility and cardiovascular disease after testosterone therapy in men with Type 2 diabetes.

Conclusion

Testosterone therapy may moderately improve sexual desire and erectile function in men with Type 2 diabetes; however, available data are limited, and the long-term risks of

> testosterone therapy are not known in this specific patient group. We conclude that testosterone therapy is a potential treatment for men with Type 2 diabetes non-responsive to phosphodiesterase-5 inhibitors. Testosterone therapy could be considered for men with Type 2 diabetes when potential risks and benefits of therapy are carefully considered and other therapeutic options are unsuitable.

ACP Journals

Clinical Guidelines | January 21, 2020

Annals of Internal Medicine®

Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA, Carrie A. Horwitch, MD, MPH, Sandeep Vijan, MD, MS, ... See More +

Author, Article and Disclosure Information

https://doi.org/10.7326/M19-0882

Eligible for CME Point-of-Care

Description:

The American College of Physicians (ACP) developed this guideline to provide clinical recommendations based on the current evidence of the benefits and harms of testosterone treatment in adult men with age-related low testosterone. This guideline is endorsed by the American Academy of Family Physicians.

Methods:

The ACP Clinical Guidelines Committee based these recommendations on a systematic review on the efficacy and safety of testosterone treatment in adult men with age-related low testosterone. Clinical outcomes were

evaluated by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system and included sexual function, physical function, quality of life, energy and vitality, depression, cognition, serious adverse events, major adverse cardiovascular events, and other adverse events.

Target Audience and Patient Population:

The target audience includes all clinicians, and the target patient population includes adult men with age-related low testosterone.

Recommendation 1a:

ACP suggests that clinicians discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function (conditional recommendation; low-certainty evidence). The discussion should include the potential benefits, harms, costs, and patient's preferences.

Recommendation 1b:

ACP suggests that clinicians should reevaluate symptoms within 12 months and periodically thereafter. Clinicians should discontinue testosterone treatment in men with age-related low testosterone with sexual dysfunction in whom there is no improvement in sexual function (conditional recommendation; low-certainty evidence).

Recommendation 1c:

ACP suggests that clinicians consider intramuscular rather than transdermal formulations when initiating testosterone treatment to improve sexual function in men with age-related low testosterone, as costs are considerably lower for the intramuscular formulation and clinical effectiveness and harms are similar.

Recommendation 2:

ACP suggests that clinicians not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition (conditional recommendation; low-certainty evidence).

Review Article | Published: 27 March 2019

What are the benefits and harms of testosterone therapy for male sexual dysfunction?—a systematic review

Konstantinos Dimitropoulos, Paolo Verze, Thomas Van den Broeck, Andrea Salonia, Cathy Yuhong Yuan, Konstantinos Hatzimouratidis & Gert Dohle

International Journal of Impotence Research **31**, 380–391 (2019)

Abstract

The role of Testosterone Therapy (TTh) in the management of male sexual dysfunction remains unclear. Objective of the authors was to systematically review the relevant literature assessing the benefits and harms of TTh in men with sexual dysfunction. EMBASE, MEDLINE, Cochrane Systematic Reviews—Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane HTA, DARE, HEED), Google Scholar, WHO international Clinical Trials Registry Platform Search Portal, CINAHL databases and clinicaltrial.gov were searched systematically in March 2015 and an updated search was performed in March 2016. Randomized and non-randomized comparative studies assessing the benefits and harms of TTh in hypogonadal, borderline eugonadal and eugonadal men suffering from sexual dysfunction were included. Risk of bias and confounding assessments were performed. A narrative synthesis was undertaken. Of the 6410 abstracts identified, 36 studies were judged to be eligible for inclusion, including 25 randomized clinical trials (RCTs) and 11 non-randomized comparative studies (NRCSs), recruiting a total of 4944 patients. RCTs were judged to have low or unclear risk of bias, while NRCSs had high risk of bias and thus, overall quality of

evidence was judged to be at least unclear. Based on the evidence mainly provided by the RCTs included in this systematic review, TTh could be considered for men with low or low-normal testosterone levels and problems with their sexual desire, erectile function and satisfaction derived from intercourse and overall sexual life. The exact testosterone formulation, dosage and duration of treatment remain to be clarified, while the safety profile of TTh also remains unclear. TTh could be used with caution in hypogonadal and most probably borderline eugonadal men to manage disorders of sexual desire, erectile function and sexual satisfaction. The overall low-to-moderate evidence quality highlights the need for robust and adequately designed clinical trials.

References

1. McCabe MP, Sharlip ID, Atalla E, Balon R, Fisher AD, Laumann E, et al. Definitions of sexual dysfunctions in women and men: A Consensus Statement From the Fourth International Consultation on Sexual Medicine 2015. J Sex Med. 2016;13:135–43. https://doi.org/10.1016/j.jsxm.2015.12.019

2. Antonio L, Wu FCW, O'Neill TW, Pye SR, Ahern TB, Laurent MR, et al. Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. J Clin Endocrinol Metab. 2016;101:2647–57. https://doi.org/10.1210/jc.2015-4106

3. O'Connor DB, Lee DM, Corona G, Forti G, Tajar A, O'Neill TW, et al. The relationships between sex hormones and sexual function in middle-aged and older European men. J Clin Endocrinol Metab. 2011;96:E1577–1587. https://doi.org/10.1210/jc.2010-2216

4. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med. 2013;10:245–84. https://doi.org/10.1111/j.1743-6109.2012.02783.x

5. Wu FCW, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363:123–35. https://doi.org/10.1056/NEJMoa0911101

6. Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. Eur Urol. 2014;65:99–112. https://doi.org/10.1016/j.eururo.2013.08.048

7. Hall SA, Esche GR, Araujo AB, Travison TG, Clark RV, Williams RE, et al. Correlates of low testosterone and symptomatic androgen deficiency in a

population-based sample. J Clin Endocrinol Metab. 2008;93:3870–7. https://doi.org/10.1210/jc.2008-0021

8. Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. J Clin Endocrinol Metab. 2017;102:1067–75. https://doi.org/10.1210/jc.2016-3580

9. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91:1995–2010. https://doi.org/10.1210/jc.2005-2847

10. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015;18:5–15. https://doi.org/10.3109/13685538.2015.1004049

11. Khera M, Adaikan G, Buvat J, Carrier S, El-Meliegy A, Hatzimouratidis K, et al. Diagnosis and treatment of testosterone deficiency: recommendations from the fourth international consultation for sexual medicine (ICSM 2015). J Sex Med. 2016;13:1787–804. https://doi.org/10.1016/j.jsxm.2016.10.009

12. NIH Consensus Conference. Impotence. NIH consensus development panel on impotence. JAMA. 1993;270:83–90.

13. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

14. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7:1–173.

15. **15.** Reeves BC, Deeks JJ, Higgins J, Wells GA Cochrane Non-Randomized Studies Methods Group. Including non-randomised studies. In: Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0. Cochrane Collaboration Web site. http://www.cochrane-handbook.org. Accessed 24 August 2017.

16. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews. A Product from the ESRC Methods Programme. (Vol. 1). Bailrigg: Lancaster University; (2006). p. 1–92.

17. Schiavi RC, White D, Mandeli J, Levine AC. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. Arch Sex Behav. 1997;26:231–41.

18. Wagner G, Rabkin J, Rabkin R. Effects of testosterone replacement therapy on sexual interest, function, and behavior in HIV+men. J Sex Res. 1997;34:27–33. https://doi.org/10.1080/00224499709551861

19. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. Arch Gen Psychiatry. 2000;57:141–7. discussion155-156

20. Gomaa A, Eissa M, El-Gebaley A. The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. Int J Impot Res. 2001;13:93–9. https://doi.org/10.1038/sj.ijir.3900643

21. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf). 2003;58:632–8.

22.

22. Dyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male. 2003;6:1–7.

23. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urology. 2004;63:641–6. https://doi.org/10.1016/j.urology.2003.11.009

24. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol. 2004;172:658–63. https://doi.org/10.1097/01.ju.0000132389.97804.d7

25. Schrader S, Mills A, Scheperle M, Block JE. Improvement in sexual functioning and satisfaction in nonresponders to testosterone gel: clinical effectiveness in hypogonadal, HIV-positive males. Clin Cornerstone. 2005;7(Suppl 4):S26–31.

26. Shamloul R, Ghanem H, Fahmy I, El-Meleigy A, Ashoor S, Elnashaar A, et al. Testosterone therapy can enhance erectile function response to sildenafil in patients with PADAM: a pilot study. J Sex Med. 2005;2:559–64. https://doi.org/10.1111/j.1743-6109.2005.00071.x

27. Steidle C, Witt MA, Matrisciano J, Block JE. Sexual functioning and satisfaction in nonresponders to testosterone gel: potential effectiveness of retreatment in hypogonadal males. Clin Cornerstone. 2005;7(Suppl 4):S20–25.

28. Merza Z, Blumsohn A, Mah PM, Meads DM, McKenna SP, Wylie K, et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. Int J Androl. 2006;29:381–91. https://doi.org/10.1111/j.1365-2605.2005.00612.x

29. **29.** Rochira V, Balestrieri A, Madeo B, Granata ARM, Carani C. Sildenafil improves sleep-related erections in hypogonadal men: evidence from a randomized, placebo-controlled, crossover study of a synergic role for both testosterone and sildenafil on penile erections. J Androl. 2006;27:165–75. https://doi.org/10.2164/jandrol.05077

30. Yassin AA, Saad F, Diede HE. Testosterone and erectile function in hypogonadal men unresponsive to tadalafil: results from an open-label uncontrolled study. Andrologia. 2006;38:61–8. https://doi.org/10.1111/j.1439-0272.2006.00712.x

31. Richardson D, Goldmeier D, Frize G, Lamba H, De Souza C, Kocsis A, et al. Letrozole versus testosterone. a single-center pilot study of HIV-infected men who have sex with men on highly active anti-retroviral therapy (HAART) with hypoactive sexual desire disorder and raised estradiol levels. J Sex Med. 2007;4:502–8. https://doi.org/10.1111/j.1743-6109.2007.00451.x

32. Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. Aging Male. 2009;12:104–12. https://doi.org/10.3109/13685530903294388

33. Herzog AG, Farina EL, Drislane FW, Schomer DL, Smithson SD, Fowler KM, et al. A comparison of anastrozole and testosterone versus placebo and testosterone for treatment of sexual dysfunction in men with epilepsy and hypogonadism. Epilepsy Behav. 2010;17:264–71. https://doi.org/10.1016/j.yebeh.2009.12.003

34. Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, Colson MH, et al. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med. 2011;8:284–93. https://doi.org/10.1111/j.1743-6109.2010.01956.x

35. Spitzer M, Basaria S, Travison TG, Davda MN, Paley A, Cohen B, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. Ann Intern Med. 2012;157:681–91. https://doi.org/10.7326/0003-4819-157-10-201211200-00004

36. Mitkov MD, Aleksandrova IY, Orbetzova MM. Effect of transdermal testosterone or alpha-lipoic acid on erectile dysfunction and quality of life in patients with type 2 diabetes mellitus. Folia Med (Plovdiv). 2013;55:55–63.

37. Park MG, Yeo JK, Cho D-Y, Kim JW, Kim JW, Oh MM, et al. The efficacy of combination treatment with injectable testosterone undecanoate and daily tadalafil for erectile dysfunction with testosterone deficiency syndrome. J Sex Med. 2015;12:966–74. https://doi.org/10.1111/jsm.12842

38. Brock G, Heiselman D, Maggi M, Kim SW, Rodríguez Vallejo JM, Behre HM, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. J Urol. 2016;195:699–705. https://doi.org/10.1016/j.juro.2015.10.083

39. Paduch DA, Polzer PK, Ni X, Basaria S. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: a randomized controlled trial. J Clin Endocrinol Metab. 2015;100:2956–62. https://doi.org/10.1210/jc.2014-4434

40. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374:611–24. https://doi.org/10.1056/NEJMoa1506119

41. Aydin S, Odabaş O, Ercan M, Kara H, Ağargün MY. Efficacy of testosterone, trazodone and hypnotic suggestion in the treatment of non-organic male sexual dysfunction. Br J Urol. 1996;77:256–60.

42.

42. Lawrence IG, Price DE, Howlett TA, Harris KP, Feehally J, Walls J. Correcting impotence in the male dialysis patient: experience with testosterone replacement and vacuum tumescence therapy. Am J Kidney Dis 1998;31:313–9.

43. Monga M, Kostelec M, Kamarei M. Patient satisfaction with testosterone supplementation for the treatment of erectile dysfunction. Arch Androl. 2002;48:433–42. https://doi.org/10.1080/01485010290099174

44. Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. Aging Male. 2003;6:86–93.

45. Greenstein A, Mabjeesh NJ, Sofer M, Kaver I, Matzkin H, Chen J. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? J Urol. 2005;173:530–2. https://doi.org/10.1097/01.ju.0000149870.36577.05

46. Hwang TI-S, Chen H-E, Tsai T-F, Lin YC. Combined use of androgen and sildenafil for hypogonadal patients unresponsive to sildenafil alone. Int J Impot Res. 2006;18:400–4. https://doi.org/10.1038/sj.ijir.3901446

47. Tas A, Ersoy A, Ersoy C, Gullulu M, Yurtkuran M. Efficacy of sildenafil in male dialysis patients with erectile dysfunction unresponsive to erythropoietin and/or testosterone treatments. Int J Impot Res. 2006;18:61–8. https://doi.org/10.1038/sj.ijir.3901372

48. Hassan A, El-Hadidy M, El-Deeck BS, Mostafa T. Couple satisfaction to different therapeutic modalities for organic erectile dysfunction. J Sex Med. 2008;5:2381–91. https://doi.org/10.1111/j.1743-6109.2007.00697.x

49. Saad F, Gooren LJ, Haider A, Yassin A. A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone

gel and parenteral testosterone undecanoate. J Androl. 2008;29:102–5. https://doi.org/10.2164/jandrol.107.002774

50. Yassin D-J, Yassin AA, Hammerer PG. Combined testosterone and vardenafil treatment for restoring erectile function in hypogonadal patients who failed to respond to testosterone therapy alone. J Sex Med. 2014;11:543–52. https://doi.org/10.1111/jsm.12378

51. Labairu-Huerta L, Padilla-Fernández B, Arrondo-Arrondo JL, Valverde-Martínez LS, Martín-Rodríguez A, Silva-Abuín JM, et al. PDE-5 inhibitors in monotherapy versus combination therapy in a sample of 1200 patients with erectile dysfunction. Arch Ital Urol Androl. 2015;87:204–9. https://doi.org/10.4081/aiua.2015.3.204

52. Yassin A, Nettleship JE, Talib RA, Almehmadi Y, Doros G. Effects of testosterone replacement therapy withdrawal and re-treatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters. Aging Male. 2016;19:64–9. https://doi.org/10.3109/13685538.2015.1126573

53. Corona G, Rastrelli G, Morgentaler A, Sforza A, Mannucci E, Maggi M.Meta-analysis of results of testosterone therapy on sexual function based on international index of erectile function scores.Eur Urol. 2017;72:1000–1011.

54. Corona G, Isidori AM, Buvat J, Aversa A, Rastrelli G, Hackett G, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med. 2014;11:1577–92. https://doi.org/10.1111/jsm.12536

55. Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf). 2005;63:381–94. https://doi.org/10.1111/j.1365-2265.2005.02350.x

56.

56. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol. 2000;164:371–5.

57. Boloña ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;82:20–8. https://doi.org/10.4065/82.1.20

58. Cunningham GR, Stephens-Shields AJ, Rosen RC, Wang C, Bhasin S, Matsumoto AM, et al. Testosterone treatment and sexual function in older men with low testosterone levels. J Clin Endocrinol Metab. 2016;101:3096–104. https://doi.org/10.1210/jc.2016-1645

59. Wu F, Zitzmann M, Heiselman D, Donatucci C, Knorr J, Patel AB, et al. Demographic and clinical correlates of patient-reported improvement in sex drive, erectile function, and energy with testosterone solution 2. J Sex Med. 2016;13:1212–9. https://doi.org/10.1016/j.jsxm.2016.05.010

60. Huo S, Scialli AR, McGarvey S, Hill E, Tügertimur B, Hogenmiller A, et al. Treatment of men for "Low Testosterone": a systematic review. PLoS ONE. 2016;11:e0162480 https://doi.org/10.1371/journal.pone.0162480

61. Tsertsvadze A, Fink HA, Yazdi F, MacDonald R, Bella AJ, Ansari MT, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med. 2009;151:650–61. https://doi.org/10.7326/0003-4819-151-9-200911030-00150

62. Gooren LJ, Behre HM. Diagnosing and treating testosterone deficiency in different parts of the world: changes between 2006 and 2010. Aging Male. 2012;15:22–7. https://doi.org/10.3109/13685538.2011.650246

63.

63. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49:822–30.

64. Derogatis LR, Melisaratos N. The DSFI: a multidimensional measure of sexual functioning. J Sex Marital Ther. 1979;5:244–81. https://doi.org/10.1080/00926237908403732

65. O'Leary MP, Fowler FJ, Lenderking WR, Barber B, Sagnier PP, Guess HA, et al. A brief male sexual function inventory for urology. Urology. 1995;46:697–706. https://doi.org/10.1016/S0090-4295(99)80304-5

66. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239–42. https://doi.org/10.1053/meta.2000.8625

67. Heinemann LAJ, Zimmermann T, Vermeulen A, Thiel C, Hummel W. A new 'aging males' symptoms' rating scale. Aging Male. 1999;2:105–14. https://doi.org/10.3109/13685539909003173

68. Cabral RD, Busin L, Rosito TE, Koff WJ. Performance of Massachusetts Male Aging Study (MMAS) and androgen deficiency in the aging male (ADAM) questionnaires in the prediction of free testosterone in patients aged 40 years or older treated in outpatient regimen. Aging Male. 2014;17:147–54. https://doi.org/10.3109/13685538.2014.908460

Author information

Affiliations

1. Department of Urology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

   Konstantinos Dimitropoulos

2. Department of Urology, University of Naples Federico II, Naples, Italy

   Paolo Verze

3. Department of Urology, University Hospitals Leuven, Leuven, Belgium

   Thomas Van den Broeck

4. Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy

   Andrea Salonia

5. Department of Medicine, McMaster University, Hamilton, ON, Canada

   Cathy Yuhong Yuan

6. Second Department of Urology, Aristotle University of Thessaloniki, Pefka, Thessaloniki, Greece

   Konstantinos Hatzimouratidis

7. Urology Department, Erasmus University Medical Center, Rotterdam, Netherlands

   Gert Dohle

Corresponding author

Correspondence to Konstantinos Dimitropoulos.

Ethics declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Additional information

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information

Supplemental 1 Search Strategy
Supplemental Table 1
Supplemental Table 2
Supplemental Table 3

Rights and permissions

Reprints and Permissions

About this article

Cite this article

Dimitropoulos, K., Verze, P., Van den Broeck, T. *et al.* What are the benefits and harms of testosterone therapy for male sexual dysfunction?—a systematic review. *Int J Impot Res* **31,** 380–391 (2019). https://doi.org/10.1038/s41443-019-0131-1

Received 05 October 2018 **Revised** 08 January 2019 **Accepted** 13 February 2019

Published 27 March 2019 **Issue Date** November 2019

DOI https://doi.org/10.1038/s41443-019-0131-1

Subjects Drug delivery • Gonadal disorders • Hormonal therapies

Further reading

- **Development of a visual tool to assess six dimensions of health and its validation in patients with endocrine disorders**
  Christian Fazekas, Dennis Linder[...] & Stefan Pilz

  Wiener klinische Wochenschrift (2021)

- **Is testosterone involved in low female sexual desire?**
  Carmita H. N. Abdo

  Archives of Endocrinology and Metabolism (2019)

International Journal of Impotence Research ISSN 1476-5489 (online)