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Premature Ejaculation and Its Association with Serum Testosterone Levels: A Comprehensive Review

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Abstract

Premature ejaculation (PE) is the most common form of male sexual dysfunction. Various hormonal and nutritional deficiencies have been implicated in PE, although conflicting data exist. We sought to determine if androgen levels, particularly testosterone, correlate with PE. A comprehensive narrative review was performed by using PubMed. Exclusion criteria included review articles and articles addressing nonandrogenic hormones. Sixty articles met our inclusion criteria and 165 were excluded. Relatively high testosterone levels were associated with PE, including men with specific medical histories (e.g., emotional trauma and infertility). On a molecular level, increased trinucleotide CAG repeats within the androgen receptor gene contributed to the relationship between high testosterone and PE. Elevated fetal androgen exposure was also linked to increased risk of PE, although the data were contradictory. In addition, although not explicitly related to high testosterone, lowering testosterone via various interventions was associated with PE improvement. Conversely, relatively low testosterone was also associated with increased risk of PE, especially when increasing testosterone through medical or surgical treatments helped alleviate PE in both human- and animal-based models. Finally, numerous studies showed no association between testosterone levels and PE, including in patients with normal or low testosterone, concurrent sexual pathologies (e.g., infertility and chronic prostatitis), comorbid chronic diseases, or various nutritional deficiencies or toxicities. The association between testosterone and PE remains controversial. Relatively high and low testosterone both appear to be associated with PE, although strong evidence exists that PE is not affected by testosterone levels. Thus, the physiologic mechanism behind PE is multifactorial and cannot be attributed solely to testosterone levels.

Keywords: premature ejaculation; testosterone; androgens; fetal

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Introduction

Premature ejaculation (PE) is the most common form of male sexual dysfunction.[1,2] Some sources estimate that >25% of patients presenting for treatment of sexual dysfunction have PE.[3,4] PE is defined as ejaculation consistently occurring within 1 min of vaginal penetration, causing great personal distress.[5,6] In patients without PE, normal intravaginal ejaculatory latency time (IELT) ranges from 5 to 20 min.[7]

There are four subtypes of PE (Table 1). Primary/lifelong PE patients experience symptoms from the start of their sexual maturity, while those with secondary/acquired PE develop the disease over the course of their life span. In terms of prevalence within the general population, primary or variable PE appears to be the most common subtype.[4,11] PE may occur in sexually active men of any age. In one study, accounting for all PE subtypes, the mean age of men presenting with PE was the midthirties, although ages ranged from 24 to 52 years.[11] Contradictory evidence exists on whether PE increases or decreases in prevalence with increasing age.[4,12]

PE is associated with several pathologies, including prostatitis, obesity, smoking, and the presence of multiple comorbidities.[4,13] In addition, numerous hormonal (e.g., leptin, melatonin, thyroid hormone, oxytocin, and prolactin) and nutritional (e.g., folate, vitamin D, magnesium, and nickel) imbalances have been implicated in PE.[14–35] Androgen levels, particularly testosterone, have also been analyzed for their role in ejaculatory physiology and PE.[36,37]

Currently, all medications used for PE treatment are considered off-label.[38,39] Standard treatment for all subtypes includes selective serotonin reuptake inhibitors (SSRIs) (e.g., "on-demand" dapoxetine), topical anesthetics, and cognitive-behavioral therapy.[19,40–43] However, certain SSRIs may negatively impact fertility or be too expensive, causing discontinuance.[44,45] In addition, some men experience PE that is refractory to SSRIs.[46] Several alternative treatments for PE have been explored with mixed results, including phenoxybenzamine, epelsiban, tadalafil, antiandrogen medications, cligosiban, and exercise.[47–52] Although many treatments exist, their beneficial mechanism often proves elusive.[53]

A better understanding of PE's etiologies will help improve treatment. The objective of this study was to determine the role of androgens, particularly testosterone, in PE.

Table 1. Subtypes of Premature Ejaculation[5,8–10]

Subtype of PE	Definition
Primary/lifelong PE	When a patient has experienced PE since beginning sexual activity
Secondary/acquired PE	When a patient develops PE after previously normal ejaculatory latency
Variable/natural variable PE	When a patient experiences PE inconsistently
Subjective PE/premature-like ejaculatory dysfunction	When a patient complains of PE, although the intravaginal ejaculatory latency time is normal

PE, premature ejaculation.

Methods

A comprehensive narrative review of PE subtypes and androgen levels was performed by using PubMed (Fig. 1). The PubMed literature review occurred from June 7, 2021, through July 2, 2021. Search fields within PubMed were considered, using MESH search terms and Boolean operators for logic syntax. The search query used was as follows: "(androgens OR testosterone OR hormones) AND premature ejaculation."

A single author (R.H.D.) performed the primary literature review. Publications were screened for title and abstract in English or English translation. Articles were reviewed for relevance to testosterone and its effect on PE as well as for scientific merit. In addition, references of excluded articles were reviewed for potential inclusion. The exclusion criteria included review articles and articles addressing nonandrogenic hormones (e.g., leptin and oxytocin).

Once initial articles were screened for inclusion, assessment of each article's relevance was made with consultation from authors J.W.G. and M.L. All disagreements on article inclusion or exclusion were discussed and resolved through consensus. No statistical or data management software was used to conduct this review.

Results

A total of 225 PubMed hits were identified on initial search. After applying the exclusion criteria, 60 articles were included in this review. Conflicting data were found on the association between serum testosterone levels and PE.

Elevated testosterone and its association with PE

Relatively high testosterone levels have been linked to PE (Table 2). Corona et al. analyzed the hormonal differences among men with acquired and lifelong PE

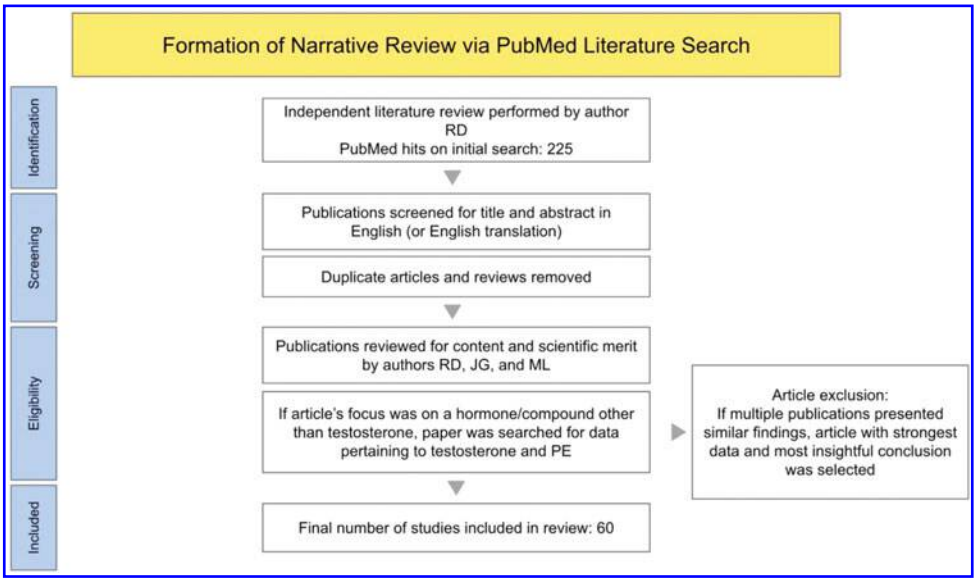

FIG. 1. Formation of narrative review via PubMed literature search.

compared with those with delayed ejaculation (DE).[54] The study included 714 patients with PE and 121 with DE. Serum hormone levels, the Structured Interview on Erectile Dysfunction questionnaire, and severity of PE/DE questionnaires were evaluated. Younger patients aged 25–39 with PE were observed to have higher total testosterone (TT) and calculated free testosterone (cFT) ($\sim$5.75 and 1.44 ng/dL, respectively) when compared with patients with DE or patients with neither PE nor DE ($p < 0.05$ for both variables). In addition, patients with lifelong PE showed statistically higher cFT than those with acquired PE.

In 2011, Corona et al. published an updated cohort and confirmed that higher TT levels were associated with increased severity of PE on multivariable analysis ($p = 0.001$), but they did not specify the PE subtype.[3]

Another study assessed 439 patients with new-onset erectile dysfunction (ED) and their comorbid sexual conditions, including PE.[55] Subjects with ED were divided into two groups: >40 and <40 years old. Two important associations were observed. First, men ≤40 years of age with ED had over two times (12.4% vs. 6.2%) the prevalence of PE ($p = 0.03$). Second, these same patients also displayed higher TT levels than men >40 years old with ED.

A similar study investigated the differences between ED and Peyronie's disease by examining 163 patients with lifelong PE age-matched to 292 patients with ED.[56] They found lifelong PE patients had higher TT than ED patients (5.38 ± 1.74 ng/mL vs. 4.89 ± 1.69 ng/mL, respectively, $p < 0.001$) and patients with neither ED nor PE (5.38 ± 1.74 ng/mL vs. 4.85 ± 1.42 ng/mL, respectively, $p < 0.001$).

Chen et al. confirmed these findings by comparing TT in PE, ED, and DE patients.[57] Patients with PE had higher TT levels (4.97 ± 1.65 ng/mL) compared with ED (4.34 ± 1.78 ng/mL) and DE patients (4.13 ± 2.11 ng/mL) ($p < 0.001$ for both comparisons). In addition, elevated TT was noted to be the sole risk factor for PE compared with control patients on multivariable analysis (odds ratio = 1.154 [95% confidence interval 1.02–1.31], $p < 0.001$]).

Relatively high testosterone was associated with PE in men with specific medical histories (Table 2). One study assessed this phenomenon in a cohort of men with couple infertility.[60] They examined 244 men with infertility and discovered the prevalence of PE in

Table 2. High Testosterone Is Associated with Premature Ejaculation

Principle	Sources
High T levels are associated with PE	3,7,36,54–59
Emotional trauma and infertility are associated with high T and PE	60,61
Increased trinucleotide CAG repeats are associated with high T and PE	62,63
Tramadol decreases T, potentially alleviating PE	64,65

T, testosterone.

their cohort was 15.6%, of which 38.5% had primary and 61.5% had secondary PE. A positive association was observed between higher cFT levels and increased premature ejaculation diagnostic tool (PEDT) scores ($r = 0.181$, $p < 0.02$).

Another study investigated the psychosocial aspect of PE via a case/control study.[61] Specifically, they evaluated the correlations between emotional traumatization, PE, and testosterone. To measure experienced trauma, the Trauma Symptoms Checklist (TSC-40) was utilized, with higher scores indicating higher levels of traumatic stress. Increased TSC-40 scores were found to be significantly associated with increased PEDT scores ($r = 0.84$) and increased cFT ($r = 0.62$). Although both PEDT scores and cFT rose with increasing TSC-40 scores, an analysis was neither performed on the effect of cFT on PEDT scores nor on the specific PE subtypes experienced by patients mentioned. Analysis was performed on TT and PEDT scores, and the result was not significant.

On the molecular level, it is theorized that increased trinucleotide CAG repeats within the androgen receptor gene (ARG) may contribute to the relationship between relatively high testosterone and PE (Table 2). One study assessed the physiologic and ejaculatory effects of CAG repeats within the ARG.[62] A total of 271 patients with primary/lifelong PE and 155 men without PE were included in this study. Peripheral blood was collected from patients to determine TT and CAG repeats within the ARG from genomic DNA.

Patients with primary PE had greater TT compared with control patients (4.91 ± 1.81 ng/mL vs. 3.8 ± 1.4 ng/mL, $p < 0.001$). TT was also negatively associated with self-estimated IELT ($r = -0.21$, $p = 0.001$). In addition, long CAG repeats (≥26 total) were significantly associated with higher TT than medium (22–25 total) and short (≤21 total) repeats (long: 5.48 ng/mL; medium: 4.23 ng/mL; short: 4.13 ng/mL; $p < 0.001$). Interestingly, the association between PEDT score and TT was not statistically significant ($r = 0.53$, $p = 0.21$).

Another study was performed in diabetic patients with acquired PE.[63] It was discovered that diabetic patients with acquired PE had higher TT than nondiabetic subjects without PE (4.76 ± 1.52 ng/mL vs. 3.63 ± 1.26 ng/mL, respectively, $p < 0.001$). TT was also inversely related to self-estimated IELT ($r = -0.024$, $p = 0.0001$). A higher number of CAG repeats were associated with higher testosterone ($r = 0.103$), higher PEDT scores ($r = 0.289$), and lower self-estimated IELT ($r = -0.168$) ($p < 0.001$ for all three variables).

Although not explicitly related to high testosterone, lowering testosterone may be associated with PE improvement (Table 2). Recent studies suggest that daily and/or precoital tramadol may be effective at treating PE.[66–69] To understand the impact of tramadol on sexual function, Kabbash et al. found a cohort of tramadol-dependent patients (TdP), 20% of whom began taking tramadol for acquired or lifelong PE.[64] TT was statistically lower in TdP than nondependent men (4.01 ± 1.63 ng/mL vs. 6.74 ± 2.21 ng/mL, respectively, $p = 0.001$). In addition, TT decreased as tramadol dosage increased ($p = 0.002$).

These data suggest that the beneficial effect of tramadol on PE may be by lowering TT, especially in those who use it on a daily basis. However, it should be noted that these TdP also had serious sexual side effects from tramadol dependence, such as decreased libido and increased ED.

A similar result was observed in an animal-based study that explored the relationship between tramadol and sexual hormones.[65] Control rats were administered 9% saline, while treatment rats received tramadol hydrochloride 40 mg/kg three times weekly for 8 weeks. Rats that received tramadol had significantly lower TT than control rats (3.78 ± 0.52 ng/mL vs. 4.21 ± 0.34 ng/mL, respectively, $p < 0.05$). The treatment group also had significantly increased testicular oxidation and diminished sperm parameters (e.g., decreased count and motility). Although the safety and efficacy of PE treatment with tramadol are controversial, these studies suggest that tramadol may have a beneficial effect on PE by lowering TT.

Decreased testosterone and its association with PE

Relatively low testosterone may be associated with increased risk of PE (Table 3). Several studies have revealed higher levels of PE in patients with low testosterone and specific demographics or comorbidities.[70–72] However, these studies often demonstrate association (e.g., percent of patients with PE and low testosterone) not causation.

For example, Tahtali investigated the hormonal parameters of patients with PE subtypes as well as patients' response to testosterone replacement therapy (TRT).[11] Of the 171 patients with PE, 48.6% had primary, 32.2% had secondary, 9.3% had variable, and 9.9% had subjective subtypes. Patients with secondary PE had significantly lower TT than other subtypes as well as the lowest IELT ($p = 0.001$ for both variables). In addition, patients with secondary PE who qualified

Table 3. Low Testosterone Is Associated with Premature Ejaculation

Patient demographics	Source
Living in Russia's southern climates	70
Living in Dhaka City with infertility	71
Hypogonadotropic hypogonadism	72
Secondary PE	11
PE improved after increased T from treatment (human models)	
Fenfluramine for hypogonadotropic hypogonadism	73
TRT for secondary PE	11
Varicocelectomy	74
PE improved after increased T from treatment (animal models)	
Satureja montana (winter savory)	75
Monsonia angustifolia (Geraniaceae)	76
Massularia acuminata root	77
Black tea brew of Camellia sinensis	78
Bulbine natalensis (Baker) stem	79

TRT, testosterone replacement therapy.

as testosterone deficient (e.g., TT <2.30 ng/mL) had shorter IELT ($p = 0.031$) and worse PEDT scores ($p = 0.044$) compared with those with normal testosterone levels.

Although not explicitly related to low testosterone, increasing serum testosterone may be associated with PE improvement (Table 3). In this same study by Tahtali, patients with secondary PE who qualified as testosterone deficient received TRT and experienced significant increases in both IELT (4.8-fold improvement, $p < 0.001$) and PEDT scores ($p = 0.002$).[11] Patients with secondary PE who were not testosterone deficient received dapoxetine treatment and experienced significant improvement in IELT (1.8-fold improvement, $p < 0.001$), but not PEDT scores ($p = 0.062$).

When the post-treatment improvements were compared between the testosterone and dapoxetine groups, both IELT ($p < 0.001$) and PEDT scores ($p = 0.001$) were better in the TRT patients. This study suggests that low serum testosterone may be associated with increased risk of secondary PE and that increasing testosterone may improve symptoms.

A similar result was seen by another study that assessed the sexual and hormonal impact of varicocelectomy in patients with PE.[74] A total of 129 varicocele patients participated in the study, 73 of whom underwent varicocelectomy (group 1) and 56 of whom were control (group 2). Before surgery, no significant difference existed in PEDT scores or TT. After surgery, the PEDT score for group 1 significantly improved (baseline: 15.56 ± 2.50, 6 months postoperatively: 11.37 ± 4.25, $p < 0.001$), yet remained the same for group 2 (baseline: 15.89 ± 2.41, 6 months later: 16.21 ± 1.85, $p = 0.159$).

In addition, TT increased in the varicocelectomy group after treatment (baseline: 331.89 ± 56.85 ng/mL, 6 months postoperatively: 357.97 ± 53.14 ng/mL, $p < 0.001$), yet remained the same in group 2 (baseline: 341.87 ± 58.92 ng/mL, 6 months later: 335.25 ± 57.11, $p = 0.055$). Furthermore, of the patients with below-normal TT levels, 62.8% had normalization postoperatively. Although the effect of TT on acquired or primary PE was not directly measured, these data suggest that PE may improve when TT is increased, especially in those with below-normal values. However, it should be noted that both the influence of varicoceles on PE and the influence of varicocelectomy on TT remain controversial.[80]

Animal-based models have also illustrated improved PE symptoms after elevation of testosterone following treatment (Table 3). One study discovered that Satureja montana (winter savory) significantly increased ejaculatory latency (EL) and raised TT in comparison with control rats ($p < 0.05$ for both variables).[75]

Another study found a similar result with Monsonia angustifolia (Geraniaceae).[76] In this study, Monsonia angustifolia was compared with sildenafil citrate (positive control) and 1% ethanol in distilled water (negative control). Both Monsonia angustifolia and sildenafil citrate increased EL and TT compared with the negative control ($p < 0.05$), and there was no significant difference in EL and TT between the two compounds. A similar increase in EL and TT was reported by Yakubu et al. with Massularia acuminata root and with Bulbine natalensis stem compared with sildenafil citrate and negative control animals.[77,79] These studies on homeopathic remedies suggest that increasing TT may aid in treating PE, although human-based models are still needed to confirm these findings.

Testosterone levels are not associated with PE

No association may exist between testosterone levels and PE (Table 4). One study showed that there was no relationship between salivary testosterone levels and ejaculation latency time (Wald $\chi^2[1] = 0.015$, $p = 0.904$) (Jern 2014).[81] Furthermore, the men in this study who ejaculated within 1 min or 1–5 min were discovered to have similar salivary testosterone levels to men who ejaculated >10 min or experienced

Table 4. Testosterone Is Not Associated with Premature Ejaculation

Purpose of study	Number of participants (*n*)	Testosterone levels	Associated with PE	Source
No association between testosterone and PE				
Assess ST levels and ELT	Patients from whom ST levels were collected: $n=384$ Patients from whom various genotype information was available: $n=1345–1429$	No significant association was found between levels of ST and ELT (Wald $\chi^2[1]=0.015$, $p=0.904$). In addition, men who ejaculated within 1 min or 1–5 min were compared with men who ejaculated >10 min or experienced anejaculation, and ST showed no difference between groups (Wald $\chi^2[1]=0.047$, $p=0.827$).	See column 3	[81]
Determine the sexual effects of 21-hydroxylase deficiency in men with CAH	Patients with CAH: $n=91$	Percent of patients with CAH and TT within the following categories: Below normal reference range: 17.3% Within normal reference range: 77.3% Above normal reference range: 5.3%	Percent of CAH patients with PE: 25.3% TT levels were not associated with alterations in sexuality (e.g., PE)	[82]
No association between low testosterone and PE				
Assess the sexual function and hormonal parameters in those with KS	Patients with KS: $n=23$ Patients without KS: $n=1363$	Patients with KS: TT: 1.73 ± 1.04 ng/mL Patents without KS: TT: 4.67 ± 1.85 ng/mL Difference of TT between groups was statistically significant ($p<0.005$)	Percent of patients with PE in those with KS: 9.5% No difference in PE rates was detected between KS patients and non-KS patients	[83]
Assess the sexual function and hormonal parameters in those with MetS	Patients without MetS: $n=567$ Patients with MetS: $n=236$	Patients without MetS Percent with hypogonadism: 3.8% cFT: 1.17 ± 0.40 ng/dL Patients with MetS Percent with hypogonadism: 11.9% cFT: 1.01 ± 0.43 ng/dL Difference of hypogonadism and cFT was statistically significant ($p<0.0001$) (note: hypogonadism defined as TT <2.31 ng/mL)	Percent of patients with PE in those with MetS: 22.7% No significant difference in PE incidence in patients with MetS vs. without MetS	[84]
Assess the sexual function and hormonal parameters in those with MetS and couple infertility	Patients with couple infertility and MetS: $n=27$ Patients with couple infertility and no MetS: $n=324$	Patients with couple infertility and MetS TT: 3.98 ± 1.87 ng/mL cFT: 8.62 ± 4.01 ng/dL Patients with couple infertility and no MetS TT: 4.82 ± 1.79 ng/mL cFT: 10.07 ± 3.37 ng/dL TT differences were statistically significant ($p<0.05$). cFT differences were statistically significant in an age-adjusted model ($p<0.001$)	Percent of patients with PE in those with MetS: 22.2% Percent of patients with PE in those without MetS: 14.4% No statistically significant difference in PE rates between groups ($p=0.283$)	[85]
Assess the sexual function and hormonal parameters in those with endocrinopathies	Patients with sexual dysfunction and no endocrinopathies: $n=951$ Patients with sexual dysfunction and endocrinopathies: $n=297$	Percent of total patients with low TT: 15% ($n=187$) Percent of total patients with normal TT: 85% ($n=1061$)	Total patients with PE: $n=476$ Percent of patients with PE and low TT: 15.3% ($n=73$) Percent of patients with PE and normal TT: 84.7% ($n=403$) No significant association found between TT and PE ($p>0.05$)	[86]

(*continued*)

Table 4. (Continued)

Purpose of study	Number of participants (*n*)	Testosterone levels	Associated with PE	Source
Assess the sexual function and hormonal parameters in those with recently diagnosed T2D	Patients with recently diagnosed (<24 months) T2D: $n=499$	17.6% of patients met EMAS criteria for hypogonadism, defined as TT <3.2 ng/mL plus ≥3 sexual symptoms (e.g., ED and reduced libido)	Risk of self-reported PE was not increased by meeting EMAS criteria ($p>0.05$)	[87]
Assess the sexual function and hormonal parameters in those with diabetes (T1D or T2D)	Patients with T1D/T2D: $n=274$	Patients with T1D/T2D and no sexual dysfunction TT: 6.7 ± 2.8 ng/mL Patients with T1D/T2D and sexual dysfunction TT: 6.0 ± 2.1 ng/mL Difference in TT was statistically significant ($p=0.025$)	Percent of patients with PE among those with sexual dysfunction: 56.6% No correlation found between PE and TT ($p>0.05$)	[88]
Assess the sexual function and hormonal parameters in those with NALD	Patients with NALD Grade A: $n=51$ Grade B: $n=18$ Grade C: $n=6$ (note: grading based on Child/Pugh classification)	Grade A TT: 6.77 ± 2.68 ng/mL cFT: 1.78 ± 0.52 ng/dL Grade B TT: 4.16 ± 1.43 ng/mL cFT: 1.06 ± 0.3 ng/dL Grade C TT: 1.78 ± 1.25 ng/mL cFT: 0.43 ± 0.18 ng/dL Differences between grades in TT and cFT were all statistically significant ($p<0.002$)	Percent of patients with PE Grade A: 33% Grade B: 40% Grade C: 67% Although PE was more prevalent in grades B and C, the differences were not statistically significant	[89]
Determine the impact of aromatase inhibition in patients with low testosterone from IHH and PE	Patients with IHH and PE: $n=10$	Before treatment TT: 4.0 ± 1.0 ng/mL cFT: 1.30 ± 0.22 ng/dL After 2 weeks of treatment with anastrozole: TT: 7.8 ± 0.9 ng/mL cFT: 2.54 ± 0.21 ng/dL Differences in both TT and cFT before vs. after treatment were statistically significant ($p<0.05$)	After 2 weeks of treatment, even after improvement of low testosterone, no improvement in PE was observed	[90]
Testosterone levels were normal in patients with PE				
Investigate the hormonal parameters in patients with PE	Patients with PE: $n=63$ Patients without PE: $n=39$	Patients with PE TT: 4.4 ± 1.7 ng/mL cFT: 1.23 ± 0.40 ng/dL Patients without PE TT: 4.5 ± 1.5 ng/mL cFT: 1.22 ± 0.33 ng/dL Differences between groups for TT and cFT were not statistically significant ($p=0.598$ and $p=0.920$, respectively)	Patients with PE had a mean PEDT score of 15.31 Patients without PE had a mean PEDT score of 5.43	[91]
Investigate the hormonal parameters in patients with PE	Patients with PE: $n=90$ Patients without PE: $n=90$	Patients with PE TT: 6.29 ± 1.76 ng/mL cFT: 2.43 ± 0.56 ng/dL Patients without PE TT: 6.23 ± 1.78 ng/mL cFT: 2.40 ± 0.54 ng/dL Differences between groups for TT and cFT were not statistically significant ($p=0.26$ and $p=0.18$, respectively)	Patients with PE had a mean PEDT score of 17.1 ± 2.37 All patients without PE had a PEDT score of <11	[92]

(*continued*)

Table 4. (Continued)

Purpose of study	Number of participants (*n*)	Testosterone levels	Associated with PE	Source
Testosterone levels remained unchanged after effective treatments for PE				
Determine the effect of dapoxetine in patients with primary PE	Patients with primary PE who completed treatment of ≥12 dapoxetine tablets: $n=56$	Patients before dapoxetine treatment TT: 3.49 ± 1.44 ng/mL Patients after dapoxetine treatment TT: 3.39 ± 1.19 ng/mL Differences between groups were not statistically significant ($p=0.088$)	Patients before dapoxetine treatment PE Arabic index: 16.9 ± 4.6 Patients after dapoxetine treatment PE Arabic index: 19.8 ± 3.9 Difference between groups was statistically significant ($p<0.001$) IELT also increased by ∼28.4 sec after treatment ($p<0.001$)	[93]
Determine the effect of venlafaxine vs. placebo in patients with PE	Patients who completed the entire crossover study and underwent data analysis: $n=21$	Before treatment, TT in all patients was within normal laboratory ranges. After treatment, no significant changes in TT were seen.	Patients before treatment with placebo/venlafaxine IELT: 60.1 ± 39.1 sec Patients after treatment with placebo IELT: 126.9 ± 98.3 sec Patients after treatment with venlafaxine IELT: 178.1 ± 122.8 IELT was significantly prolonged after treatment in both placebo and venlafaxine groups ($p<0.0001$). No significant difference was seen comparing IELT after treatment in placebo vs. venlafaxine ($p=0.144$)	[94]
Determine the effect of GB on sexual function, including PE	Patients who received GB: $n=59$ Patients who received placebo: $n=59$	Before 8-week treatment Patients who received GB: TT: 5.00 ± 1.90 ng/mL Patients who received placebo: TT: 4.82 ± 1.71 ng/mL After 8-week treatment Patients who received GB: TT: 4.99 ± 1.68 ng/mL Patients who received placebo: TT: 4.69 ± 1.54 ng/mL Differences in TT for both GB and placebo were not statistically significant before vs. after treatment ($p=0.94$ and $p=0.52$, respectively)	Before 8-week treatment Patients who received GB: PEDT score: 9.14 ± 4.57 Patients who received placebo: PEDT score: 10.46 ± 4.79 After 8-week treatment Patients who received GB: PEDT score: 7.53 ± 4.26 Patients who received placebo: PEDT score: 9.66 ± 4.57 Difference between GB PEDT scores before vs. after treatment was significant ($p=0.001$). Difference between placebo PEDT scores before vs. after treatment was not significant ($p=0.177$). Difference between GB and placebo PEDT scores after 8-week treatment was significant ($p=0.017$).	[95]

CAH, congenital adrenal hyperplasia; cFT, calculated free testosterone; ED, erectile dysfunction; EMAS, European Male Aging Study; GB, ginseng berries; IELT, intravaginal ejaculation latency time; IHH, idiopathic hypogonadotropic hypogonadism; KS, Klinefelter syndrome; MetS, metabolic syndrome; NALD, nonalcoholic liver disease; PEDT, premature ejaculation diagnostic tool; ST, salivary testosterone; T2D, type 2 diabetes; TT, total testosterone.

anejaculation (Wald $\chi^2[1] = 0.047$, $p = 0.827$). Another study reported that 25.3% of patients with congenital adrenal hyperplasia had lifelong PE and varying levels of TT.[82] However, these varying levels of TT had no effect on sexuality (e.g., risk of PE), satisfaction with sex life, or sexual activity.

Low testosterone levels were not associated with an increased risk of PE (Table 4). Corona et al. investigated sexual dysfunction and hormonal parameters in those men with Klinefelter syndrome (KS).[83] They found that KS men had significantly less TT compared with controls (TT in patients with KS: 1.73 ± 1.04 ng/mL, TT in patients without KS: 4.67 ± 1.85 ng/mL, $p < 0.005$). However, after adjusting for age, the incidence of lifelong PE between the two groups was not statistically different.

A similar result was seen when comparing patients with metabolic syndrome (MetS) compared with patients without MetS.[85] In this study, both groups were experiencing couple infertility. Although the TT and cFT levels were lower in those with MetS, the rate of PE was similar between groups (PE in patients with MetS: 22.2%, PE in patients without MetS: 14.4%, $p = 0.283$). However, this study did not discern PE subtypes within their cohort.

In addition, another study investigated the effect of increasing testosterone levels on acquired PE in patients with low testosterone from idiopathic hypogonadotropic hypogonadism.[90] After a 2-week treatment with 1 mg/day of anastrozole (an aromatase inhibitor), both TT and cFT levels increased. However, no difference was seen in PE before versus after treatment, suggesting low testosterone was not the cause of PE.

Patients with PE were found to have normal testosterone levels (Table 4). Canat et al. investigated the hormonal profile of patients with either lifelong or acquired PE compared with patients without PE.[91] Although patients with PE had several hormones (e.g., thyroid-stimulating hormone, luteinizing hormone [LH], and prolactin) that were statistically lower compared with the reference population, no difference was seen with TT or cFT. A similar result was observed by another study in which TT and cFT levels were not statistically different between those with and those without lifelong or acquired PE.[92] However, in this second study, there was also no statistically significant difference in LH, prolactin, or follicle-stimulating hormone (FSH) between the groups.

PE was treated by various interventions that had no effect on testosterone levels (Table 4). One study evaluated the effectiveness of dapoxetine treatment in patients with primary PE.[93] Patients were required to take at least 12 "on-demand" tablets of 30 mg dapoxetine. On follow-up, both IELT and PE Arabic index increased after treatment, although testosterone remained unchanged. However, it should be noted that the changes in both IELT and PE Arabic index were minor, although still statistically significant.

Kiliç et al. performed a similar study, testing venlafaxine in patients with PE but did not specify the subtype of PE.[94] Specifically, they did a randomized, single-blind, placebo-controlled, crossover study in which patients received 75 mg of venlafaxine HCl extended release or placebo pill for 2 weeks, followed by a washout period of 1 week, and a subsequent crossover period for an additional 2 weeks. After treatment with either placebo or venlafaxine, IELT was significantly increased, although the increase was the same for both placebo and venlafaxine. Pre- and post-treatment TT remained unchanged in both groups. Of note, this study used a cutoff of <2 min to define PE, rather than the usual <1 min.

Another study analyzed the effects of ginseng berries (GB) on sexual function, including PE.[95] Patients who received GB had improved PEDT scores at 4- and 8-week follow-up visits; patients who received placebo did not have improved PEDT scores. However, TT remained unchanged for both groups at both the 4- and 8-week visits.

Testosterone was normal in patients with PE and various sexual pathologies (Table 5). Mazzilli et al. assessed the incidence of ejaculatory dysfunction in infertile men.[96] They found that 16 out of 3280 had PE (0.5%), although TT was normal in all cases. A similar study also observed that infertile patients were more likely to experience PE compared with fertile couples (PEDT scores were >8 in 12.9% of infertile couples vs. 4.1% of fertile couples, $p = 0.036$).[97] However, TT and cFT did not differ significantly between groups.

One study analyzed hormonal parameters and rates of ED in patients with chronic prostatitis.[98] They reported that PEDT scores increased in the ED group compared with patients without ED (9.98 ± 4.76 vs. 7.43 ± 4.76, respectively, $p = 0.003$). However, TT did not differ between patients with or without ED (3.81 ± 1.65 ng/mL vs. 4.37 ± 1.54 ng/mL, respectively, $p = 0.056$).

Another study evaluated sexual function in men with late-onset hypogonadism.[100] Patients were divided into two groups based on if they had a positive Androgen Deficiency in Aging Males questionnaire

Table 5. Normal Testosterone Levels in Patients with Premature Ejaculation and Other Comorbidities

Comorbidity	Sources
Sexual health pathologies	
Infertility	96,97
Erectile dysfunction with chronic prostatitis	98
Postorgasmic illness syndrome	99
Late-onset hypogonadism with ADAM positive questionnaire	100
Chronic diseases	
Type 1 diabetes	101
Metabolic syndrome	102
Advanced chronic kidney disease	103
Generalized epilepsy	104
Psychiatric illnesses	
Anxiety	105
Alcoholism	106
Miscellaneous pathologies	
COVID-19 infection	107
Restless leg syndrome	108
Folate deficiency	24
Nickel toxicity	34

ADAM, androgen deficiency in the aging male; COVID-19, coronavirus disease 2019.

(group 1) or negative questionnaire (group 2.) They reported that 38.7% of group 1 had a PEDT score ≥9 compared with only 10.9% of group 2 ($p < 0.001$), although the mean TT was not statistically different between the groups.

Testosterone was normal in patients with chronic diseases and PE (Table 5). Caruso et al. investigated the sexual effects of type 1 diabetes and found that the prevalence of acquired PE and ED in this population was 13% and 25%, respectively.[101] They also observed that age, diabetes duration, and severity of depression all had positive correlations with PEDT score ($p < 0.001$ for all three variables.) Average TT level for type 1 diabetics was normal (6.81 ± 1.50 ng/mL).

Another study showed that patients with secondary PE had an increased prevalence of MetS compared with a healthy control group (% of MetS patients with acquired PE: 18.9%; % of MetS patients without acquired PE: 10.2%, $p = 0.019$).[102] The TT between those men with acquired PE and those without was not statistically different (TT in patients with acquired PE: 5.08 ± 1.74 ng/mL vs. 5.03 ± 1.68 ng/mL in those without acquired PE, $p = 0.833$). It should be noted that the IELT used in this study to define PE was <3 min.

Elbardisi et al. assessed the sexual health of those with advanced chronic kidney disease (ACKD).[103] They discovered that 88.24% of patients with ACKD had acquired PE and that the incidence of PE was significantly correlated with increased age and ED ($p < 0.001$ for both variables). The TT level was not a risk factor for PE in this population.

Testosterone was normal in PE patients with various deficiencies or toxicities (Table 5). One study investigated the hormonal and nutritional status of patients presenting with ED, acquired PE, and PE combined with ED.[24] Patients with lower folate levels were observed to be at increased risk of ED, PE, and PE combined with ED, although TT levels proved similar between all three groups.

Beshir et al. investigated the hormonal parameters, nickel content, and sexual dysfunction rates in men employed as electroplaters.[34] They found that factory workers had increased urinary nickel, LH, FSH, and PE rates compared with controls. However, the TT levels in those exposed and those not exposed were not statistically different. These studies suggest that toxicities and deficiencies unrelated to testosterone may affect PE.

Fetal androgen exposure and its association with PE

Fetal androgen exposure (FAE) and its association with primary PE may be assessed by analyzing second-to-fourth digit (2D:4D) ratios in adult male hands. In adult males, the 2D (index finger) is usually shorter in length than 4D (ring finger), while females have equal 2D and 4D or longer 2D lengths.[109] Thus, the fetal testosterone/estradiol ratio is negatively correlated with 2D:4D in male hands.[110] A small 2D:4D ratio is also associated with less CAG trinucleotide repeats in the ARG, representing increased androgen sensitivity.[111]

After determining that patient demographics were similar (e.g., age, body habitus, and TT levels), Bolat et al. found that self-estimated IELT was positively correlated with 2D:4D ratios (right hand: $r = 0.258$, $p = 0.003$; left hand: $r = 0.240$, $p = 0.006$), demonstrating that IELT was extended if less testosterone exposure occurred *in utero*.[112] Furthermore, PEDT scores had a negative association with digit ratios (right hand: $r = -0.363$, $p = 0.003$; left hand: $r = -0.238$, $p = 0.006$). Interestingly, adult TT levels were not significantly associated with IELT or PEDT score ($r = 0.043$, $p = 0.624$; $r = 0.025$, $p = 0.777$, respectively). These data suggest that increased FAE is a risk factor for primary PE.

Another study tested whether the 2D:4D ratio was associated with PE, ED, and/or online sexual compulsivity (OSC).[113] Poor control over ejaculation, an

element of PE, was discovered in 5% of pornography-consuming patients. Interestingly, the 2D:4D ratio was determined to not affect ejaculatory control, yet increased OSC was associated with less control over ejaculation. These results contradict the results from Bolat et al., in which a decreased 2D:4D ratio was associated with more severe PE. Therefore, further studies are needed to determine if 2D:4D ratios predict risk of PE.

Investigating FAE by assessing anogenital distance (AGD) is controversial. In men, AGD is 2×longer than in women.[114] Animal and human studies suggest that increased AGD is associated with higher FAE, although the data are inconsistent.[115–117] Toprak et al. surmised that AGD was increased in men with lifelong PE ($p = 0.01$).[118] They also determined a positive correlation between PEDT scores and AGD as well as a negative correlation between IELT and AGD ($r = 0.199$, $p = 0.019$; $r = -0.185$, $p = 0.028$, respectively). No significant relationship was seen between AGD, PEDT, or IELT and adult TT levels.

A similar study was performed in which patients with PE were noted to have a shorter AGD ($p < 0.001$).[119] The authors concluded that their results were similar to Toprak's results, in that altered AGD was associated with PE. However, to better understand the relationship between PE and FAE, further research is needed to elucidate if AGD is increased or decreased in patients with PE.

Limitations

While 60 publications were selected for inclusion, this study was limited by only capturing articles from one database (PubMed). In addition, many studies included in this review were retrospective in nature with few randomized, controlled trials. Our conclusions are therefore limited by the current quality of published literature. However, many studies included a large number of patients from which to draw meaningful conclusions.

Conclusion

Contemporary evidence for the association between testosterone and PE remains controversial. This may, in part, be due to the large patient heterogeneity and poor PE subtyping within the published literature. In addition, many studies use relative values for determining high versus low testosterone in patients with PE rather than using laboratory-based testosterone ranges. This makes it difficult to determine a specific value that would qualify as low or high testosterone when assessing risk for PE.

Currently, relatively high serum testosterone appears to be associated with increased risk of PE. This may be linked to a genetic alteration in ARG, but research into this connection is still developing. Relatively low testosterone appears to only be minimally associated with PE in select patient populations. However, low testosterone is clinically known to profoundly affect erectile health and libido. Therefore, it is reasonable to infer that decreased testosterone may disrupt erectile function, leading to PE. In addition, a strong association did exist between increased relatively low values of testosterone via treatment (e.g., TRT and fenfluramine) and improved PE.

Numerous studies showed that testosterone may not be related to PE risk or treatment. FAE and its association with PE are still underdeveloped, although an association may exist. Thus, the physiologic mechanism underlying PE is multifactorial and cannot be attributed solely to testosterone levels.

Further studies using laboratory-based testosterone ranges are needed to assess if low versus high testosterone is truly related to PE. In addition, large multicentered prospective studies into the treatment of relatively low and high testosterone are needed to fully assess the utility of androgen modulation in PE patients.

We recommend that, at the discretion of each health care provider, measuring serum testosterone levels and other hormone panels may be useful in PE patients. Evaluating serum testosterone may be especially beneficial in patients with PE refractory to standard treatments. In several studies, patients with low testosterone and PE showed improvement in symptoms after TRT. In addition, patients with high testosterone showed improved PE after various testosterone-lowering treatments (e.g., tramadol). Thus, after taking testosterone levels into account, select patients should be counseled on a case-by-case basis for possible testosterone-altering PE therapies.

Authors' Contributions

Conception and design: R.H.D., J.W.G., M.L., and W.J.G.H. Acquisition and analysis of data: R.H.D., J.W.G., and M.L. Writing—original draft: R.H.D., J.W.G., M.L., and W.J.G.H. Writing—revision: J.W.G. and R.H.D. Final approval: R.H.D., J.W.G., M.L., and W.J.G.H.

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References

1. Althof SE, McMahon CG, Waldinger MD, 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. 2014;11(6):1392–1422.
2. Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, Alexander J. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: Prevalence, comorbidities, and professional help-seeking. Eur Urol. 2007;51(3): 816–823.
3. Corona G, Jannini EA, Lotti F, et al. Premature and delayed ejaculation: Two ends of a single continuum influenced by hormonal miliefu. Int J Androl. 2011;34(1):41–48.
4. Gao J, Zhang X, Su P, et al. Prevalence and factors associated with the complaint of premature ejaculation and the four premature ejaculation syndromes: A large observational study in China. J Sex Med. 2013;10(7): 1874–1881.
5. Serefoglu EC, McMahon CG, Waldinger MD, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: Report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. J Sex Med. 2014;11(6): 1423–1441.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, 5th ed. Arlington, VA: American Psychiatric Publishing. 2013.
7. Zhao J, Ma Y, Zhai X, Li H, Wang Z, Chong T. Elevated free testosterone levels and reduced very low-density lipoprotein levels in men with lifelong premature ejaculation: A preliminary study. J Int Med Res. 2021; 49(4):3000605211002681.
8. Waldinger MD. Premature ejaculation: State of the art. Urol Clin North Am. 2007;34(4):591-viii.
9. Gajjala SR, Khalidi A. Premature ejaculation: A review. Indian J Sex Transm Dis AIDS. 2014;35(2):92–95.
10. McMahon CG, Jannini E, Waldinger M, Rowland D. Standard operating procedures in the disorders of orgasm and ejaculation. J Sex Med. 2013; 10(1):204–229.
11. Tahtali İN. Is testosterone replacement an effective treatment of secondary premature ejaculation? Andrologia. 2020;52(1):e13452.
12. Corona G, Rastrelli G, Maseroli E, Forti G, Maggi M. Sexual function of the ageing male. Best Pract Res Clin Endocrinol Metab. 2013;27(4):581–601.
13. Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA. Prevalence of chronic prostatitis in men with premature ejaculation. Urology. 2001;58(2):198–202.
14. Nikoobakht MR, Tajik P, Karami AA, Moradi K, Mortazavi A, Kosari F. Premature ejaculation and serum leptin level: A diagnostic case-control study. J Sex Med. 2008;5(12):2942–2946.
15. Wang B, Yang C, Tang K. Serum leptin and 5-hydroxytryptamine measurements for the diagnosis and treatment of premature ejaculation. Urology. 2013;82(6):1336–1340.
16. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Semercioz A. Serum leptin levels in patients with premature ejaculation before and after citalopram treatment. BJU Int. 2003;91(3):252–254.
17. Tang KL, Wang BL, Yang L, Li LM, Zhou Y, Yang CH. Sexual function improvement in association with serum leptin level elevation in patients with premature ejaculation following sertraline treatment: A preliminary observation. Bosn J Basic Med Sci. 2013;13(4):248–252.
18. Atmaca M, Kuloglu M, Tezcan E, Semercioz A, Ustundag B, Ayar A. Serum leptin levels in patients with premature ejaculation. Arch Androl. 2002; 48(5):345–350.
19. Kirecci SL, Simsek A, Gurbuz ZG, et al. Relationship between plasma melatonin levels and the efficacy of selective serotonin reuptake inhibitors treatment on premature ejaculation. Int J Urol. 2014;21(9):917–920.
20. Amano T. Editorial Comment from Dr Amano to Relationship between plasma melatonin levels and the efficacy of selective serotonin reuptake inhibitors treatment on premature ejaculation. Int J Urol. 2014;21(9):921.
21. Sato Y. Editorial Comment from Dr Sato to Relationship between plasma melatonin levels and the efficacy of selective serotonin reuptake inhibitors treatment on premature ejaculation. Int J Urol. 2014;21(9):920.
22. Canat L, Degirmentepe RB, Atalay HA, et al. Low serum vitamin D is associated with an increased likelihood of acquired premature ejaculation. Int Braz J Urol. 2019;45(3):621–628.
23. Abd El Aal AM, GamalEl Din SF, Rashed LA, Tawfik AERB, ElSheemy MS. Serum vitamin D level may be a novel potential risk factor for premature ejaculation: A comparative study. Int Urol Nephrol. 2018;50(11):1975–1980.
24. Yan WJ, Yu N, Yin TL, Zou YJ, Yang J. A new potential risk factor in patients with erectile dysfunction and premature ejaculation: Folate deficiency. Asian J Androl. 2014;16(6):902–906.
25. Cahangirov A, Cihan A, Murat N, et al. Investigation of the neural target level of hyperthyroidism in premature ejaculation in a rat model of pharmacologically induced ejaculation. J Sex Med. 2011;8(1):90–96.
26. Bates JN, Kohn TP, Pastuszak AW. Effect of thyroid hormone derangements on sexual function in men and women. Sex Med Rev. 2020;8(2): 217–230.
27. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab. 2005;90(12):6472–6479.
28. Omu AE, Al-Bader AA, Dashti H, Oriowo MA. Magnesium in human semen: Possible role in premature ejaculation. Arch Androl. 2001;46(1): 59–66.
29. Wayman C, Russell R, Tang K, et al. Cligosiban, a novel brain-penetrant, selective oxytocin receptor antagonist, inhibits ejaculatory physiology in rodents. J Sex Med. 2018;15(12):1698–1706.
30. Gul M, Serefoglu EC. Oxytocin antagonists: The next frontier in PE treatment. Nat Rev Urol. 2019;16(12):696–697.
31. Jern P, Westberg L, Johansson A, et al. Are single nucleotide polymorphisms in the oxytocin and vasopressin 1A/1B receptor genes likely candidates for variation in ejaculatory function? BJU Int. 2012;110(11 Pt C):E1173–E1180.
32. Gupta J, Russell R, Wayman C, Hurley D, Jackson V. Oxytocin-induced contractions within rat and rabbit ejaculatory tissues are mediated by vasopressin V1A receptors and not oxytocin receptors. Br J Pharmacol. 2008;155(1):118–126.
33. Clément P, Peeters M, Bernabé J, Denys P, Alexandre L, Giuliano F. Brain oxytocin receptors mediate ejaculation elicited by 7-hydroxy-2-(di-N-propylamino) tetralin (7-OH-DPAT) in anaesthetized rats. Br J Pharmacol. 2008;154(5):1150–1159.
34. Beshir S, Ibrahim KS, Shaheen W, Shahy EM. Hormonal perturbations in occupationally exposed nickel workers. Open Access Maced J Med Sci. 2016;4(2):307–311.
35. Rastrelli G, Corona G, Maggi M. The role of prolactin in andrology: What is new? Rev Endocr Metab Disord. 2015;16(3):233–248.
36. Mohseni MG, Hosseini SR, Alizadeh F, Rangzan N. Serum testosterone and gonadotropins levels in patients with premature ejaculation: A comparison with normal men. Adv Biomed Res. 2014;3:6.
37. Vignozzi L, Corona G, Petrone L, et al. Testosterone and sexual activity. J Endocrinol Invest. 2005;28(3 Suppl.):39–44.
38. Rew KT. Men's health: Male sexual dysfunction. FP Essent. 2021;503: 28–33.
39. Fallon B. 'Off-label' drug use in sexual medicine treatment. Int J Impot Res. 2008;20(2):127–134.
40. Jannini EA, Ciocca G, Limoncin E, et al. Premature ejaculation: Old story, new insights. Fertil Steril. 2015;104(5):1061–1073.
41. Karsenty G, Marcelli F, Robin G, et al. Les médicaments de la médecine sexuelle [Drugs for sexual medicine] [published correction appears in Prog Urol. 2013 Dec;23(16):1455. Geoffroy, R [corrected to Robin, Geoffroy]]. Prog Urol. 2013;23(15):1299–1311.
42. Porst H. Reflexionen über 50 Jahre Sexualmedizin in der Urologie mit Fokus auf männliche Sexualstörungen [Reflexions on 50 Years of Sexual Medicine in Urology Focusing on Male Sexual Dysfunctions]. Aktuelle Urol. 2019;50(3):248–267.
43. Du Y, Jiang Y, Zhang J, et al. Efficacy and safety of "on-demand" dapoxetine in treatment of patients with premature ejaculation: A meta-analysis. Med Sci Monit. 2019;25:4225–4232.
44. ElMazoudy R, AbdelHameed N, ElMasry A. Paternal dapoxetine administration induced deterioration in reproductive performance, fetal outcome, sexual behavior and biochemistry of male rats. Int J Impot Res. 2015;27(6):206–214.

45. International Society for Sexual Medicine. Available at https://www.issm.info/news/sex-health-headlines/dapoxetine-for-premature-ejaculation-has-high-discontinuation-rate/ (accessed December 8, 2021).
46. Janssen PK, Touw D, Schweitzer DH, Waldinger MD. Nonresponders to daily paroxetine and another SSRI in men with lifelong premature ejaculation: A pharmacokinetic dose-escalation study for a rare phenomenon. Korean J Urol. 2014;55(9):599–607.
47. Homonnai ZT, Shilon M, Paz GF. Phenoxybenzamine—An effective male contraceptive pill. Contraception. 1984;29(5):479–491.
48. Shinghal R, Barnes A, Mahar KM, et al. Safety and efficacy of epelsiban in the treatment of men with premature ejaculation: A randomized, double-blind, placebo-controlled, fixed-dose study. J Sex Med. 2013;10(10):2506–2517.
49. Karabakan M, Keskin E, Akdemir S, Bozkurt A. Effect of tadalafil 5mg daily treatment on the ejaculatory times, lower urinary tract symptoms and erectile function in patients with erectile dysfunction. Int Braz J Urol. 2017;43(2):317–324.
50. Kilinc MF, Aydogmus Y, Yildiz Y, Doluoglu OG. Impact of physical activity on patient self-reported outcomes of lifelong premature ejaculation patients: Results of a prospective, randomised, sham-controlled trial. Andrologia. 2018;50(1):10.
51. Wiederholt I. Behandlung de Ejaculatio Praecox mit einem Antiandrogen [Treatment of premature ejaculation with an antiandrogen]. Psychiatr Prax. 1977;4(3):176–180.
52. Althof S, Osterloh IH, Muirhead GJ, George K, Girard N; PEDRIX Multi-Centre Study Group. The oxytocin antagonist cligosiban fails to prolong intravaginal ejaculatory latency in men with lifelong premature ejaculation: Results of a randomized, double-blind, placebo-controlled phase iib trial (PEDRIX). J Sex Med. 2019;16(8):1188–1198.
53. LoPiccolo J. Diagnosis and treatment of male sexual dysfunction. J Sex Marital Ther. 1985;11(4):215–232.
54. Corona G, Jannini EA, Mannucci E, et al. Different testosterone levels are associated with ejaculatory dysfunction. J Sex Med. 2008;5(8):1991–1998.
55. Capogrosso P, Colicchia M, Ventimiglia E, et al. One patient out of four with newly diagnosed erectile dysfunction is a young man—Worrisome picture from the everyday clinical practice. J Sex Med. 2013;10(7):1833–1841.
56. Wu F, Chen T, Mao S, Jiang H, Ding Q, Xu G. Levels of estradiol and testosterone are altered in Chinese men with sexual dysfunction. Andrology. 2016;4(5):932–938.
57. Chen T, Wu F, Wang X, et al. Different levels of estradiol are correlated with sexual dysfunction in adult men. Sci Rep. 2020;10(1):12660.
58. Culha MG, Tuken M, Gonultas S, Cakir OO, Serefoglu EC. Frequency of etiological factors among patients with acquired premature ejaculation: Prospective, observational, single-center study. Int J Impot Res. 2020;32(3):352–357.
59. Oztürk Mİ, Koca O, Tüken M, Keleş MO, Ilktaç A, Karaman MI. Hormonal evaluation in premature ejaculation. Urol Int. 2012;88(4):454–458.
60. Lotti F, Corona G, Rastrelli G, Forti G, Jannini EA, Maggi M. Clinical correlates of erectile dysfunction and premature ejaculation in men with couple infertility. J Sex Med. 2012;9(10):2698–2707.
61. Fiala L, Lenz J. Psychosocial stress, somatoform dissociative symptoms and free testosterone in premature ejaculation. Andrologia. 2020;52(11):e13828.
62. Khan HL, Bhatti S, Abbas S, et al. Serotonin transporter (5-HTTLPR) genotypes and trinucleotide repeats of androgen receptor exert a combinatorial effect on hormonal milieu in patients with lifelong premature ejaculation. Andrology. 2018;6(6):916–926.
63. Khan HL, Bhatti S, Abbas S, et al. Longer trinucleotide repeats of androgen receptor are associated with higher testosterone and low oxytocin levels in diabetic premature ejaculatory dysfunction patients. Basic Clin Androl. 2018;28:3.
64. Kabbash A, El Kelany R, Oreby M, El Gameel D. Effect of tramadol dependence on male sexual dysfunction. Interdiscip Toxicol. 2019;12(4):157–162.
65. Ahmed MA, Kurkar A. Effects of opioid (tramadol) treatment on testicular functions in adult male rats: The role of nitric oxide and oxidative stress. Clin Exp Pharmacol Physiol. 2014;41(4):317–323.
66. Martyn-St James M, Cooper K, Kaltenthaler E, et al. Tramadol for premature ejaculation: A systematic review and meta-analysis. BMC Urol. 2015;15:6.
67. Ur Rehman MF, Imran Zaidi A, Ul Haq T, Rafique S, Ali F. Comparison of the efficacy of tramadol and paroxetine in the management of premature ejaculation. Cureus. 2020;12(9):e10725.
68. Hamidi-Madani A, Motiee R, Mokhtari G, Nasseh H, Esmaeili S, Kazemnezhad E. The efficacy and safety of on-demand tramadol and paroxetine use in treatment of life long premature ejaculation: A randomized double-blind placebo-controlled clinical trial. J Reprod Infertil. 2018;19(1):10–15.
69. Sharma AP, Sharma G, Tyagi S, et al. Safety and efficacy of "on-demand" tramadol in patients with premature ejaculation: An updated meta-analysis. Int Braz J Urol. 2021;47(5):921–934.
70. Kul'chavenia EV, Azizov AP, Romanovskiĭ MD, et al. [Ejaculatory disorders in some regions of the Russian Federation]. Urologiia. 2010;(3):49–52.
71. Khondker L, Khan SI, Ahamed RS. Profile of infertility status of male in Dhaka city. Mymensingh Med J. 2012;21(3):456–461.
72. Cohen PG. The association of premature ejaculation and hypogonadotropic hypogonadism. J Sex Marital Ther. 1997;23(3):208–211.
73. Cohen PG, Holbrook JM. Effects of fenfluramine on ejaculatory function, luteinizing hormone and testosterone levels in men with hypogonadotropic hypogonadism and premature ejaculation. Int Clin Psychopharmacol. 1999;14(2):91–94.
74. Ahmed AF, Abdel-Aziz AS, Maarouf AM, Ali M, Emara AA, Gomaa A. Impact of varicocelectomy on premature ejaculation in varicocele patients. Andrologia. 2015;47(3):276–281.
75. Zavatti M, Zanoli P, Benelli A, Rivasi M, Baraldi C, Baraldi M. Experimental study on Satureja montana as a treatment for premature ejaculation. J Ethnopharmacol. 2011;133(2):629–633.
76. Fouche G, Afolayan AJ, Wintola OA, Khorombi TE, Senabe J. Effect of the aqueous extract of the aerial parts of Monsonia angustifolia on the sexual behaviour of male Wistar rats. BMC Complement Altern Med. 2015;15:343.
77. Yakubu MT, Awotunde OS, Ajiboye TO, Oladiji AT, Akanji MA. Pro-sexual effects of aqueous extracts of Massularia acuminata root in male Wistar rats. Andrologia. 2011;43(5):334–340.
78. Ratnasooriya WD, Fernando TS. Effect of black tea brew of Camellia sinensis on sexual competence of male rats. J Ethnopharmacol. 2008;118(3):373–377.
79. Yakubu MT, Afolayan AJ. Effect of aqueous extract of Bulbine natalensis (Baker) stem on the sexual behaviour of male rats. Int J Androl. 2009;32(6):629–636.
80. Kose O, Ozbek E. Re: Ahmed et al.: Impact of varicocelectomy on premature ejaculation (PE) in varicocele patients. Andrologia. 2015;47(6):603.
81. Jern P, Westberg L, Ankarberg-Lindgren C, et al. Associations between salivary testosterone levels, androgen-related genetic polymorphisms, and self-estimated ejaculation latency time. Sex Med. 2014;2(3):107–114.
82. Gehrmann K, Engels M, Bennecke E, et al. Sexuality in males with congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency. J Endocr Soc. 2019;3(8):1445–1456.
83. Corona G, Petrone L, Paggi F, et al. Sexual dysfunction in subjects with Klinefelter's syndrome. Int J Androl. 2010;33(4):574–580.
84. Corona G, Mannucci E, Schulman C, et al. Psychobiologic correlates of the metabolic syndrome and associated sexual dysfunction. Eur Urol. 2006;50(3):595–604.
85. Lotti F, Corona G, Degli Innocenti S, et al. Seminal, ultrasound and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples. Andrology. 2013;1(2):229–239.
86. El-Sakka AI, Hassoba HM, Sayed HM, Tayeb KA. Pattern of endocrinal changes in patients with sexual dysfunction. J Sex Med. 2005;2(4):551–558.
87. Corona G, Giorda CB, Cucinotta D, Guida P, Nada E; Gruppo di studio SUBITO-DE. Sexual dysfunction at the onset of type 2 diabetes: The interplay of depression, hormonal and cardiovascular factors. J Sex Med. 2014;11(8):2065–2073.
88. Owiredu WK, Amidu N, Alidu H, Sarpong C, Gyasi-Sarpong CK. Determinants of sexual dysfunction among clinically diagnosed diabetic patients. Reprod Biol Endocrinol. 2011;9:70.
89. Zifroni A, Schiavi RC, Schaffner F. Sexual function and testosterone levels in men with nonalcoholic liver disease. Hepatology. 1991;14(3):479–482.
90. Holbrook JM, Cohen PG. Aromatase inhibition for the treatment of idiopathic hypogonadotropic hypogonadism in men with premature ejaculation. South Med J. 2003;96(6):544–547.

91. Canat L, Erbin A, Canat M, Dinek M, Caskurlu T. Assessment of hormonal activity in patients with premature ejaculation. Int Braz J Urol. 2017; 43(2):311–316.
92. Abu El-Hamd M, Farah A. Possible role of serum testosterone, gonadotropins and prolactin in patients with premature ejaculation. Andrologia. 2018;50(1):e12808.
93. Kati B, Ay H. Evaluation of dapoxetine treatment success in lifelong premature ejaculation patients with penile sympathetic skin response. Andrologia. 2018;50(9):e13076.
94. Kiliç S, Ergin H, Baydinç YC. Venlafaxine extended release for the treatment of patients with premature ejaculation: A pilot, single-blind, placebo-controlled, fixed-dose crossover study on short-term administration of an antidepressant drug. Int J Androl. 2005;28(1):47–52.
95. Choi YD, Park CW, Jang J, et al. Effects of Korean ginseng berry extract on sexual function in men with erectile dysfunction: A multicenter, placebo-controlled, double-blind clinical study. Int J Impot Res. 2013; 25(2):45–50.
96. Mazzilli R, Defeudis G, Olana S, Zamponi V, Macera M, Mazzilli F. The role of ejaculatory dysfunction on male infertility. Clin Ter. 2020;171(6):e523–e527.
97. Lotti F, Corona G, Castellini G, et al. Semen quality impairment is associated with sexual dysfunction according to its severity. Hum Reprod. 2016;31(12):2668–2680.
98. Fan D, Mao W, Wang G, et al. Study on the relationship between sex hormone changes and erectile dysfunction in patients with chronic prostatitis/chronic pelvic pain syndrome. Ann Palliat Med. 2021;10(2): 1739–1747.
99. Jiang N, Xi G, Li H, Yin J. Postorgasmic illness syndrome (POIS) in a Chinese man: No proof for IgE-mediated allergy to semen. J Sex Med. 2015;12(3):840–845.
100. Lee MH, Seo DH, Lee CW, et al. Relationship between hypogonadal symptoms, sexual dysfunction and chronic prostatitis in middle-aged men by self-reported questionnaires, even without biochemical testosterone deficiency. World J Mens Health. 2020;38(2):243–249.
101. Caruso P, Cirillo P, Carbone C, et al. Sexual dysfunctions and short-term glucose variability in young men with type 1 diabetes [published online ahead of print, 2021 Apr 30]. Hormones (Athens). 2021;20(3): 475–482.
102. Jeh SU, Yoon S, Choi JH, et al. Metabolic syndrome is an independent risk factor for acquired premature ejaculation. World J Mens Health. 2019;37(2):226–233.
103. Elbardisi H, Majzoub A, Daniel C, et al. Endocrine contribution to the sexual dysfunction in patients with advanced chronic kidney disease and the role of hyperprolactinemia [published online ahead of print, 2021 Jun 5]. Andrologia. 2021:e14135.
104. Hamed S, Mohamed K, El-Taher A, Hamed E, Omar H. The sexual and reproductive health in men with generalized epilepsy: A multidisciplinary evaluation. Int J Impot Res. 2006;18(3):287–295.
105. Corona G, Mannucci E, Petrone L, et al. Psycho-biological correlates of free-floating anxiety symptoms in male patients with sexual dysfunctions. J Androl. 2006;27(1):86–93.
106. Fahrner EM. Sexual dysfunction in male alcohol addicts: Prevalence and treatment. Arch Sex Behav. 1987;16(3):247–257.
107. Salama N, Blgozah S. COVID-19 and male sexual functioning: A report of 3 recovered cases and literature review. Clin Med Insights Case Rep. 2021;14:11795476211020593.
108. Kurt O, Yazici CM, Alp R, Sancak EB, Topcu B. Is it only a sleeping disorder or more? Restless legs syndrome and erectile function. Scand J Urol. 2016;50(5):392–395.
109. Hönekopp J, Watson S. Meta-analysis of digit ratio 2D:4D shows greater sex difference in the right hand. Am J Hum Biol. 2010;22(5):619–630.
110. Lutchmaya S, Baron-Cohen S, Raggatt P, Knickmeyer R, Manning JT. 2nd to 4th digit ratios, fetal testosterone and estradiol. Early Hum Dev. 2004; 77(1–2):23–28.
111. Manning J, Bundred PE, Newton DJ, Flanagan BF. The second to fourth digit ratio and variation in the androgen receptor gene. Evol Hum Behav. 2003;24(6):399–405.
112. Bolat D, Kocabas GU, Kose T, Degirmenci T, Aydin ME, Dincel C. The relationship between the second-to-fourth digit ratios and lifelong premature ejaculation: A prospective, comparative study. Andrology. 2017;5(3):535–540.
113. Buchholz VN, Mühle C; Cohort Study on Substance Use Risk Factors, Kornhuber J, Lenz B. Markers of prenatal androgen exposure correlate with online sexual compulsivity and erectile function in young men. Front Psychiatry. 2021;12:517411.
114. Thankamony A, Ong KK, Dunger DB, Acerini CL, Hughes IA. Anogenital distance from birth to 2 years: A population study. Environ Health Perspect. 2009;117(11):1786–1790.
115. Macleod DJ, Sharpe RM, Welsh M, et al. Androgen action in the masculinization programming window and development of male reproductive organs. Int J Androl. 2010;33(2):279–287.
116. Dean A, Smith LB, Macpherson S, Sharpe RM. The effect of dihydrotestosterone exposure during or prior to the masculinization programming window on reproductive development in male and female rats. Int J Androl. 2012;35(3):330–339.
117. Bornehag CG, Carlstedt F, Jönsson BA, et al. Prenatal phthalate exposures and anogenital distance in Swedish boys. Environ Health Perspect. 2015;123(1):101–107.
118. Toprak T, Şahin A, Akgul K, et al. The relationship between anogenital distance and lifelong premature ejaculation. Andrology. 2020;8(2): 353–357.
119. Sertkaya Z, Ertaş K, Tokuç E. The relationship between premature ejaculation and anogenital distance. Andrologia. 2020;52(6):e13571.

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Abbreviations Used

ACKD = advanced chronic kidney disease
ADAM = androgen deficiency in the aging male
AGD = assessing anogenital distance
ARG = androgen receptor gene
CAH = congenital adrenal hyperplasia
cFT = calculated free testosterone
COVID-19 = coronavirus disease 2019
DE = delayed ejaculation
ED = erectile dysfunction
EL = ejaculatory latency
ELT = ejaculatory latency times
EMAS = European Male Aging Study
FAE = fetal androgen exposure
FSH = follicle-stimulating hormone
GB = ginseng berries
IELT = intravaginal ejaculatory latency time
IHH = idiopathic hypogonadotropic hypogonadism
KS = Klinefelter syndrome
LH = luteinizing hormone
MetS = metabolic syndrome
NALD = nonalcoholic liver disease
OSC = online sexual compulsivity
PE = premature ejaculation
PEDT = premature ejaculation diagnostic tool
SSRIs = selective serotonin reuptake inhibitors
ST = salivary testosterone
T2D = type 2 diabetes
TdP = tramadol-dependent patients
TRT = testosterone replacement therapy
TSC-40 = Trauma Symptoms Checklist
T = testosterone
TT = total testosterone