Epidemiology of delayed ejaculation

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Abstract: A large body of literature on diminished ejaculatory disorders has been generated without the use of a clear diagnostic definition. Many studies have not distinguished between the orgasm and ejaculation disorders leading to doubtful results. Delayed ejaculation (DE) is one of the diminished ejaculatory disorders, which range from varying delays in ejaculatory latency to a complete inability to ejaculate. The present review is aimed at providing a comprehensive overview of the current knowledge on the definition and epidemiology of diminished ejaculatory disorders. We focus on the acquired diseases, such as benign prostatic hyperplasia (BPH) and specific drug regimens that may cause an iatrogenic form of ejaculatory disorder. In addition, the impact of aging is discussed since the prevalence of DE appears to be moderately but positively related to age. Finally, we also focus on the importance of the hormonal milieu on male ejaculation. To date, evidence on the endocrine control of ejaculation is derived from small clinical trials, but the evidence suggests that hormones modulate the ejaculatory process by altering its overall latency.

Keywords: Testosterone; thyroid stimulating hormone (TSH); lower urinary tract symptoms (LUTS); delayed ejaculation (DE); retrograde ejaculation (RE); anejaculation; anorgasmia; painful ejaculation

Introduction

Of the main categories of male sexual dysfunction, delayed ejaculation (DE) has received the least attention even though it can lead to marked distress or interpersonal difficulties (1). DE is one of the diminished ejaculatory disorders, which range from varying delays in ejaculatory latency to a complete inability to ejaculate, and include DE, retrograde ejaculation (RE), anejaculation, anorgasmia and painful ejaculation (2).

DE, or ejaculatory insufficiency, is an inhibition of the ejaculatory reflex, with absent or reduced seminal emission and impaired ejaculatory contractions, possibly with impaired or absent orgasm. Men with DE may be able to ejaculate with great effort and after prolonged intercourse or are unable to ejaculate in some circumstances. The symptom can occur both during intercourse and with manual stimulation in the presence or absence of a partner (relative or absolute DE, respectively). DE can be defined as lifelong, from the first sexual experience, or acquired, i.e., subsequent to a normal period of sexual functioning (2).

There are not definite criteria for evaluating men complaining of DE. Based on the fact that the median value of intravaginal ejaculatory latency time (IELT) was 5.4 minutes (3) and 21–23 min represents about two standard deviations above the mean, we assume that men

with latencies beyond 25 or 30 minutes suffer from DE (4,5).

Conversely, according to the Diagnostic and Statistical Manual of Mental Disorders, 5ᵗʰ edition (DSM-V) (6), there is no set time threshold for what defines DE.

In fact, DSM-V defines DE as a marked delay in ejaculation or a marked infrequency or absence of ejaculation on almost all or all occasions (75–100% of the time) of partnered sexual activity without the individual desiring delay, persisting for at least 6 months and causing significant distress to the individual.

Psychological causes of DE are constituted by fear and anxiety during sex, childhood sexual abuse, sexual trauma, repressive sexual education, religious beliefs, sexual and general anxiety, and relationship difficulties (5).

Among biological factors, these may include specific pharmacologic agents, including antidepressants (especially selective serotonin reuptake inhibitors SSRIs), antipsychotics and opioids, or endocrine diseases (7,8). A particularly severe form of DE is represented by anejaculation, or impotentia ejaculationis (2), which is when a man is unable to ejaculate through any form of stimulation, masturbation or coitus. Anejaculation appears to be mainly caused by organic aetiologies, including ejaculatory duct obstruction, extirpative pelvic surgery (e.g., prostatectomy), pelvic trauma, pelvic radiation, neurological diseases and diabetes.

RE occurs when there is a sensation of orgasm and contraction of the ischeo- and bulbocavernosus muscles at the base of the penis, but no semen is ejaculated. This is due to an incomplete closure of the bladder's internal sphincter leading to back ejaculation into the bladder (retrograde). Patients may complain of a dry ejaculation followed by "white urine" when voiding. RE is often due to iatrogenic causes, but in many cases, diabetes or other organic pathologies could be the main aetiology (1). Anorgasmia is defined as the perceived absence of orgasm, independent of the presence of ejaculation, and this sexual dysfunction can be a lifelong or acquired problem.

A aetiological factors for anorgasmia include substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear (1).

In rare subjects, orgasm may alter central neurotransmission, provoking a post-ejaculatory pain syndrome (9) or the post-orgasmic illness syndrome, which is characterised by severe fatigue, intense warmth and a flu-like state, with generalised myalgia (10).

The present review provides an overview of the current knowledge on the epidemiology of diminished ejaculatory disorders, with a focus on the acquired disease in specific populations at higher risk of developing DE and other forms of ejaculatory disorders.

Epidemiology

The lack of a consistent definition of DE and variations in the research methodology accounts for the different prevalence rates reported.

Noting that ejaculation dysfunctions are also an infrequent precipitant of medical or sexological consultations (11-13).

There seems to be a general agreement that the prevalence of DE is low and ranges from 1% (lifelong DE) to 4% (acquired DE) of sexually active men (2,14).

However, contrary to old reported percentages, more recent population surveys (15) and cross-sectional observations (16-19) have reported that, like erectile dysfunction (ED) and premature ejaculation (PE), DE and other diminished ejaculatory dysfunctions are common forms of male sexual dysfunction. Hence, the limited and old reported percentages probably underestimate the actual incidence.

Specifically, the above studies have reported that certain demographic and clinical factors correlate with ejaculatory dysfunctions. For example, DE appears to be positively related to age (20-24) and the prevalence differs among races (16,19).

Also, the frequencies of ejaculatory dysfunction increased with increasing ED severity (19). Similarly, patients taking SSRIs, and endocrine diseases are also associated with DE (25,26).

The true incidence of RE is also difficult to estimate. It ranges from 0.3% to 2% of patients attending fertility clinics (27), but it may increase in patients with diabetes. Diabetes causes disruption of sexual functions via the following two mechanisms: autonomic neuropathy, which causes ED and ejaculatory dysfunction, and concurrent vascular disease, which is a major cause of ED. Ejaculatory dysfunction can exhibit a slow progressive decline from a DE-RE to anejaculation, depending on the degree of sympathetic autonomic neuropathy involved (28). It has been observed a 6% incidence of RE in 54 diabetic patients with sexual dysfunction (mean age: 36 years) (27) and a correlation between ejaculatory dysfunction and peripheral autonomic disorders was observed by demonstrating anhydrosis in five diabetic patients with RE (29). In a more recent study, RE was demonstrated in 34.6% of diabetic men (30). To date, the true incidence of RE among diabetics is difficult to ascertain. There is a high likelihood that a significant percentage of

diabetic males with ejaculatory disorders go unrecognised because they impregnate their partners prior to developing this disorder or do not desire children. However, if a diabetic patient presents himself with male factor infertility, a detailed history concerning the patient's sexual habits and ejaculatory ability should be obtained.

Anejaculation occurs in 0.14% of the general population, according to Kinsey (31). The incidence of anejaculation is highest in men with spinal cord injury (SCI), diabetes mellitus, myelitis or multiple sclerosis, with the first being the most common cause. In fact, after SCI most men cannot ejaculate without medical assistance. Ejaculation occurred in response to masturbation or coitus, penile vibratory stimulation (PVS) or acetylcholine esterase inhibitors (AchEi) followed by masturbation in, respectively, 11.8%, 47.4% and 54.7% of patients with complete SCI and in, respectively, 33.2%, 52.8% and 78.1% of patients with incomplete SCI. Ejaculation, in the case of complete lesion of the sympathetic centres (T12 to L2), of the parasympathetic and somatic centres (S2–S4) or of all spinal ejaculation centres (T12 to S5) occurred in response to PVS in none of the patients and in response to AchEi followed by masturbation in 4.9%, 30.8% and 0% of the patients, respectively (32).

Effects of aging on ejaculatory function

The prevalence of DE appears to be moderately and positively related to age, which is not surprising in view of the fact that ejaculatory function as a whole tends to diminish as men age.

The results of a community-based study of 1,688 men in the Netherlands showed that the prevalence of ejaculatory dysfunctions (defined as ejaculation with a decreased amount of semen or anejaculation) increased from 3% in men aged 50–54 years to 35% in those aged 70–78 years (20).

In a longitudinal analysis from the Olmsted County Study of 1,547 men aged 40–70 years, sex drive, erectile function, ejaculatory function, problem assessment and overall satisfaction worsened with increasing age (21).

The Global Study of Sexual Attitudes and Behaviours (GSSAB) was an international survey involving 13,882 women and 13,618 men, aged 40–80 years, in order to systematically study factors that may contribute to the aetiology of sexual problems. In the GSSAB study, the prevalence of sexual dysfunction is quite high and tends to increase with age, especially in men. The estimated prevalence of inability to reach orgasm in men was around 10% and greatly increased with age (odd ratio up to 7.7). The real prevalence of DE in GSSAB is not clear because the definition, used for ejaculatory disorders, refers to the inability to achieve orgasm. This definition may include not only DE, but also anejaculation and anorgasmia (33).

An age-dependent increase in the prevalence of DE was reported in an Italian study in which patients with DE were older than those reporting PE (50.4 ± 13.2 vs. 48.3 ± 12.8 years old; $P<0.05$). Knowing that DE and PE represent two ends of a linear spectrum, ejaculatory disorders were reported as a spectrum with a score ranging from 0 (anejaculation/severe DE) to 7 (severe PE). High scores (i.e., shorter IELT) progressively decreased as a function of age, suggesting that in advanced age more men complain of DE than of PE (22). Paduch and coauthors (16) evaluated for associations of demographic factors such as age as possible correlates of ejaculatory dysfunction. The authors bring out an age-associated increase of perceived ejaculate volume reduction (PEVR) and/or decreased force of ejaculation (DFE). Prevalence of PEVR increases in men after the age of 40 years, and the odds of experiencing the symptom were three times higher in men aged 60–70 years compared with men <40 years. Similarly, odds of experiencing DFE were approximately three times higher in men aged 60–70 years compared with men aged <40 years.

In the very well conducted European Male Ageing Study (EMAS), advancing age and increasing comorbidities were associated with greater prevalence rates of ejaculatory dysfunctions. EMAS is the largest multicentre, population-based study of aging in European men and has allowed to systematically analyse different aspects of both general and sexual health in a sample of 3,369 men aged 40–79 years old (mean, 60 ± 11 years). Overall, about half of the subjects were overweight and more than 50% of them reported one or more morbidities (hypertension, obesity and heart diseases). Around 6% of men reported severe orgasmic impairment that was closely associated with age and concomitant morbidities (23).

Consistent with the results of EMAS, the National Social Life, Health, and Aging Project (NSHAP) reported the prevalence of sexual activity, behaviours and problems in a representative group of the US general population of 3,005 adults (1,550 women and 1,455 men; 57–85 years of age), and described the association of these variables with age and health status. NSHAP indicated that physical health is more strongly associated with many sexual problems than age alone (24).

Hormonal regulation of ejaculation function

Thyroid hormones

Thyroid stimulating hormone (TSH) levels were positively related to reported ejaculatory latencies (18). The association between thyroid disease and some sexual symptoms, such as PE in hyperthyroidism, DE in hypothyroidism, and hypoactive sexual desire (HSD) and ED in both conditions, have been extensively documented, even in an animal model (26,34,35).

We evaluated the efficacy of thyroid treatment in hypothyroid patients with DE (21). In a series of 14 subjects with hypothyroidism, the prevalence of HSD, DE and ED was 64.3%, whereas the prevalence of PE was 7.1%. In seven of 14 hypothyroid men, HSD was associated with DE, and in six, DE was associated with ED. In patients with hypothyroidism, among which PE was nearly absent, a resolution of DE was obtained in half of the subjects after thyroid hormone normalisation. In men with hypothyroidism, IELT decreased significantly from 21.8 ± 10.9 to 7.4 ± 7.2 min (P<0.01). Interestingly, this reduction was found in hypothyroid patients that were complaining of DE at baseline and in those who were not.

The view that thyroid hormones regulate the ejaculatory reflex is emerging and hypothyroidism should be ruled out in each patient with DE (26). Waldinger did not find any association between TSH levels and IELT in a cohort of Dutch subjects (3) with lifelong PE. This is not surprising since thyroid diseases are usually well cured in western societies, with normalization of TSH levels. Hence, a correlation between lifelong PE and thyroid diseases cannot be found, not searched.

Testosterone

Different T levels can be related to different subsets of ejaculatory disturbances. In particular, DE is associated with lower levels of T. A consecutive series of 2,437 (mean age: 51.9 ± 13.0 years), male patients with sexual dysfunction were studied in order to evaluate the possible contribution of T and hypogonadism to the ejaculatory reflex by comparing subjects with PE or DE to those without ejaculatory dysfunction. Among the patients studied, 714 (25.9%) and 121 (4.4%) reported PE and DE, respectively. In the youngest age band (25–40 years), subjects with PE reported higher total T (TT) and free T (FT) levels when compared to the other groups (subjects with DE or those without PE and DE; P<0.05 for both). Conversely, in the oldest

age band (55–70 years), lower TT and FT levels were observed in DE subjects. Accordingly, patients with PE showed the lowest (12%) and subjects with DE the highest (26%) prevalence of hypogonadism. These differences were confirmed even after adjustment for confounders such as age and libido [HR=0.75 (0.57–0.99) and 1.83 (1.14–3.94) for PE and DE, respectively; both P<0.05] (17). These results were confirmed by a further study that showed that low T levels and the presence of hypogonadism symptoms are associated with an overall lower propensity to ejaculate. Specifically, a consecutive series of 2,693 patients seeking medical care for sexual dysfunction were retrospectively evaluated. Among the patients studied, T level progressively decreased from patients with severe PE to those with anejaculation. Moreover, patients with DE had a higher prevalence of hypogonadism. Prolactin (PRL) and TSH levels progressively increased from patients with severe PE to those with anejaculation (22).

Furthermore, low T levels reduce ejaculate volume (18). A progressive increase in severity of PEVR was associated with lower T levels. Accordingly, a higher prevalence of hypogonadism was observed in patients with PEVR compared with the rest of the sample without hypogonadism (9.1% vs. 5.3%; P<0.05 after adjustment for age, BMI and smoking habits). Conversely, in a double-blind, randomized, placebo-controlled, 16-week trial with T solution 2% versus placebo (36), T replacement was not associated with significant improvement in ejaculatory dysfunction in androgen-deficient men. Interestingly, the same authors (16) always showed that high T levels increased the odds of DE. Hence, it seems that more research is still needed regarding the role of T in ejaculation disorders.

Prolactin

Hyperprolactinemia (HPRL) has been associated with DE and anorgasmia, which was mostly ED related.

Systematic determination of serum PRL found a very low prevalence of HPRL in ED patients (1–5%). Compiling the ten largest series leads to a prevalence of 0.62% for severe HPRL (serum PRL: >35 ng/mL) and 0.4% for pituitary adenomas among 8,700 ED patients. The prevalence of mild HPRL (serum PRL: 20–35 ng/mL) in male subjects with sexual dysfunction is quite variable, ranging from more than 13% to less than 2%. In one of the largest studies published so far, involving 2,146 patients with sexual dysfunction, mild HPRL was found in 69 (3.3%) and severe HPRL in 32 (1.5%) cases (37).

Isolated RE has also been reported in patients with HPRL. The mechanism of ejaculatory failure in association with HPRL is speculative, but raised levels of PRL may affect bladder neck closure during ejaculation and lead to RE (38). Furthermore, high levels of PRL may reflect a central dopaminergic derangement, with could, in turn, reduce the ability to ejaculate (39,40).

In contrast to HPRL, PRL in the lowest quartile is associated with PE and anxiety symptoms, as well as with metabolic syndrome and arteriogenic ED (41).

Measurement of PRL levels can be considered in patients with anejaculation or DE and in presence of antidopaminergic treatments or symptoms of HPRL.

Oxytocin

In rats, oxytocin (OX) showed a facilitator effect on ejaculation by reducing the ejaculatory latency time and post-coital refractory time; on the other hand, rodents with lower OX levels had longer mount and refractory times, providing further demonstration of a role for this hormone during ejaculation. However, administration of exogenous OX did not show the expected results: in a small group of healthy men, intranasal application of OX did not have any significant effect on sexual behaviour, and hence, more studies are needed to determine the effect of oxytocin on ejaculation in men (42,43).

Effects of lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) in ejaculatory dysfunction

LUTS, including urinary frequency, urgency, decreased urine flow rates and nocturnal, are common problems in aging individuals. BPH is the primary cause of LUTS in men aged 50 years and older (44).

Large-scale epidemiologic studies with different population samples have demonstrated consistent evidence of a relationship between LUTS and ejaculation disorders in aging men that is independent of age and other comorbidities. The Asian Survey of Aging Males, which surveyed 1,155 men aged 50–80 years, demonstrated a LUTS prevalence of 14–59% and an ejaculation disorders (defined as ejaculation with a decreased amount of semen volume or anejaculation) prevalence of 68% (45). Similar to that found in the Multinational Survey of the Aging Male (MSAM-7) (15), moderate or severe LUTS was an independent risk factor for ejaculation disorders after adjusting for age and comorbidities, being men with

severe LUTS 3.3 times more likely to report ejaculation disorders.

A significant positive association was found between reduced ejaculation and LUTS after adjusting for age in a urology clinic-based sample of men from 12 countries (46). In Italian men with LUTS/BPH, lower urinary tract symptoms were significantly associated with ejaculation disorders by multivariate logistic regression analysis (47). LUTS was a strong predictor of reduced volume of ejaculate and pain/discomfort on ejaculation after adjusting for age, body mass index, previous BPH surgery, comorbidities, and antihypertensive medication use in a multinational study of men with LUTS/BPH (48). Furthermore, treatment of LUTS suggestive of BPH can be associated with side effects on ejaculation function. Surgical interventions for LUTS/ BPH, including transurethral resection of the prostate (TURP), may cause RE and anejaculation. According to a single-arm meta-analysis conducted by the American Urological Association (49), the estimated incidence of ejaculation disorders with TURP was 65% in 19 trials. The corresponding rate of ejaculation disorders was 59% for transurethral holmium laser resection/enucleation prostatectomy (two trials), 17% for transurethral laser coagulation (17 trials), 18% for transurethral incision of the prostate (11 trials), 65% for transurethral electro vaporization (6 trials), 42% for transurethral laser vaporization (5 trials), and 61% for open prostatectomy (1 trial). A randomised controlled trial reported by Brookes evaluated the amount of semen during ejaculation and anejaculation at baseline and 6–12 months after TURP, non-contact laser therapy, or watchful waiting in 340 men aged 48–90 years with LUTS/BPH. The percentage of men with ejaculation disorders was significantly increased from baseline after TURP, laser therapy and watchful waiting (all P<0.005) (50).

Anejaculation and decreased ejaculate volume is associated with tamsulosin and silodosin, which are super selective α_1-adrenergic receptor antagonists. Ejaculation disorders are rare with α_1-adrenergic receptor antagonists that are not super selective for the α_1-adrenergic receptor subtype, namely alfuzosin, doxazosin and terazosin. Treatment with the 5-reductase inhibitor finasteride or dutasteride is associated with ejaculation disorders and other types of sexual dysfunction (51).

A significantly higher incidence of anejaculation was demonstrated in men receiving tamsulosin (11%) than in those receiving placebo (1%). With silodosin the incidence of ejaculatory dysfunction was 28.1% vs. 1.1%.

The incidence of anejaculation was low and similar in the alfuzosin group and the placebo group (0.6% *vs.* 0%). Moreover, with doxazosin, the incidence was 0.4% *vs.* 1.4% for ejaculatory disorders (51).

Treatment with finasteride, a selective inhibitor of 5a-reductase type 2, is generally well tolerated, but side effects related to sexual function occur significantly more frequently in men, especially young, treated for 1 year with finasteride than in those receiving placebo. Moreover, the incidence of ejaculatory disorders was 8% for finasteride-treated patients versus 2% for placebo-treated patients (52). Patients treated with dutasteride in three randomised, double-blind, clinical trials experienced significantly higher incidence rates of RE and anejaculation (2% *vs.* 1% for the placebo group) (53).

Conclusions

A large body of literature on diminished ejaculatory disorders has been generated without the use of a clear diagnostic definition. It must be emphasised that in many studies, there is no clear distinction between the orgasm and ejaculation disorders. Furthermore, there is a paucity of information concerning the severity of complaint criteria (e.g., delayed *vs.* absent). The lack of use of accurate measurement tools, such as a stopwatch to measure ejaculation time, further limit our knowledge about the exact prevalence. Taken together, these data suggest that the prevalence may be underestimated and, in order to look for the percentage of men really affected, it should be mandatory to use an operational criteria definition.

Few studies on lifelong DE and anorgasmia are available since they are poorly described, and have been historically considered to have a low rate in the general population and in clinical practice.

Conversely, the high prevalence of acquired ejaculatory dysfunctions should be emphasised. Medical conditions that may lead to acquired DE or anejaculation include SCI and neurodegenerative disorders, for example, multiple sclerosis or diabetic neuropathy. A wide range of drugs can impair ejaculation through central and peripheral mechanisms. Again, the acquired ejaculatory dysfunctions predominate in specific selected populations of men.

As men age, a moderate delay in ejaculation occurs. Prevalence estimates vary with the definition used and the population studied, but overall around 6% of men aged >50 years report ejaculatory impairment. Ejaculatory dysfunctions in the aged male are most probably due to several comorbidities, including metabolic and cardiovascular disorders, increased prevalence of T deficiency, increased use of medications, and decreased exercise. In effect, advancing age and increasing comorbidities were associated with greater prevalence of ejaculatory dysfunction (up to 35% in those aged 70–78 years). These data highlight that during the entire lifespan, but in particular in old age, sexual issues should be adequately addressed by investigating illnesses that might contribute to sexual problems.

After adjusting for age and common comorbidities, ejaculatory dysfunctions were significantly associated with LUTS and men with severe LUTS were 3.3 times more likely to report ejaculation disorders. Moreover, rates of ejaculatory diseases with TURP are ~65%, with the vast majority losing ante grade ejaculation. This has a significant negative impact on quality of life, not only in regard to orgasmic function, but also for fertility, considering the relatively early onset of BPH. However, because of the increase in life expectancy, physicians should discuss sexual function with their patients who have LUTS/BPH, especially when selecting a BPH treatment and when monitoring the effects of BPH treatment.

Finally, this article has also focused on the importance of the hormonal milieu on male ejaculation. To date, evidence on the endocrine control of ejaculation is derived from small clinical trials, but the evidence suggests that hormones modulate the ejaculatory process by altering its overall latency.

We and others (22) identified relationships between ejaculation and PRL, TSH and T levels. Being DE and PE two ends of a linear spectrum, it has been shown that PRL and TSH levels progressively increase from patients with PE to those with DE, and the opposite is true for T. Hence, we suggest the evaluation of T, PRL and thyroid functioning only when significant symptoms indicating underlying diseases are present. Further studies are advisable in order to confirm these results.

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Footnote

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