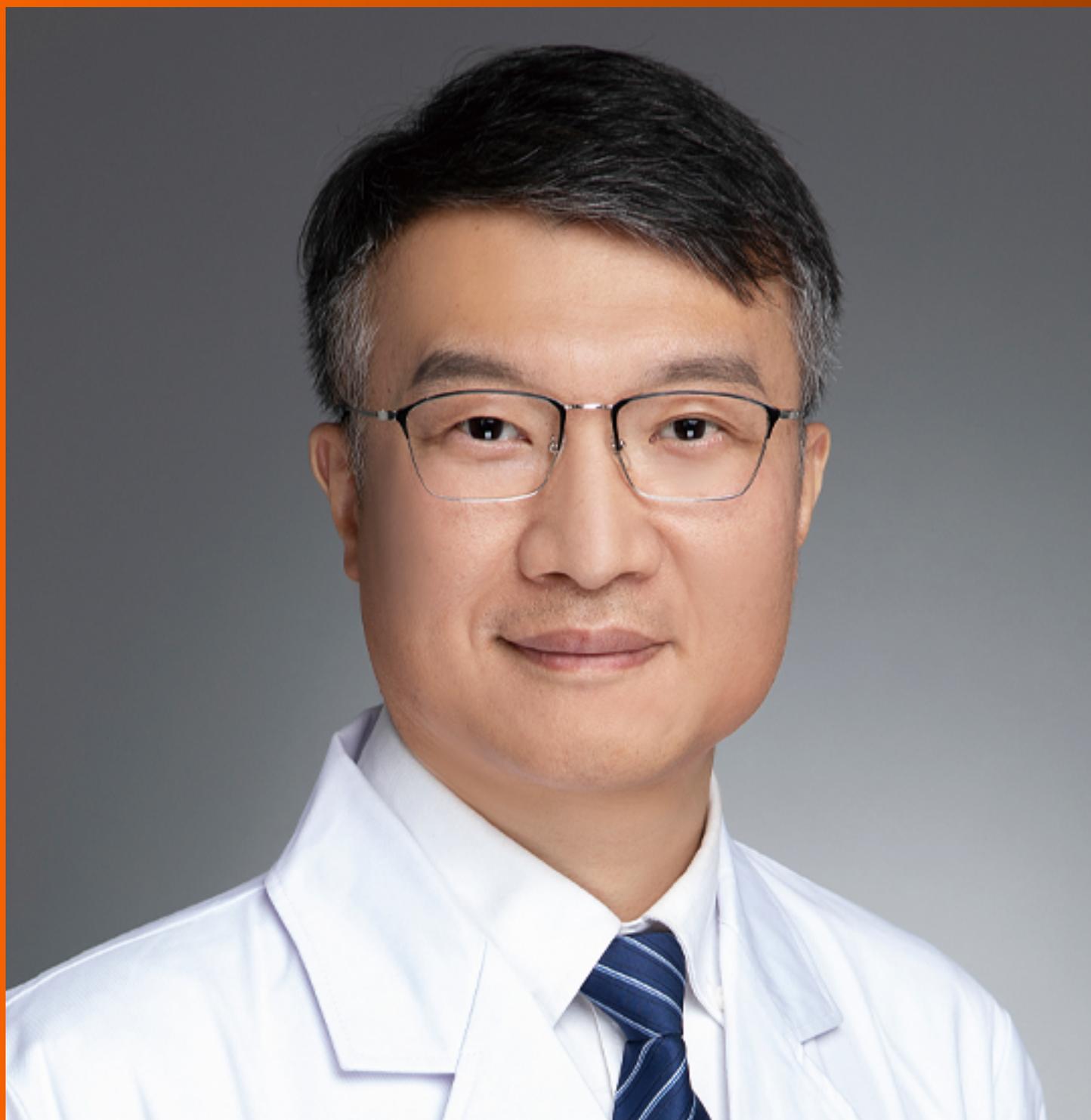


World Journal of *Diabetes*

World J Diabetes 2021 July 15; 12(7): 916-1140



FIELD OF VISION

- 916 Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind
Infante M, Leoni M, Caprio M, Fabbri A

OPINION REVIEW

- 932 Exploring new treatment options for polycystic ovary syndrome: Review of a novel antidiabetic agent SGLT2 inhibitor
Marinkovic-Radosevic J, Cigrovski Berkovic M, Kruezi E, Bilic-Curcic I, Mrzljak A

REVIEW

- 939 Role of interferons in diabetic retinopathy
Li BY, Tan W, Zou JL, He Y, Yoshida S, Jiang B, Zhou YD
- 954 Ejaculatory dysfunction in men with diabetes mellitus
Mostafa T, Abdel-Hamid IA
- 975 Diabetic patients with chronic kidney disease: Non-invasive assessment of cardiovascular risk
Piko N, Bevc S, Ekart R, Petreski T, Vodošek Hojs N, Hojs R
- 997 Mechanisms of altered bone remodeling in children with type 1 diabetes
Brunetti G, D'Amato G, De Santis S, Grano M, Faienza MF
- 1010 Current cancer therapies and their influence on glucose control
Yim C, Mansell K, Hussein N, Arnason T
- 1026 Immunometabolic bases of type 2 diabetes in the severity of COVID-19
Viurcos-Sanabria R, Escobedo G
- 1042 Spatial epidemiology of diabetes: Methods and insights
Cuadros DF, Li J, Musuka G, Awad SF
- 1057 Comprehensive overview of human serum albumin glycation in diabetes mellitus
Qiu HY, Hou NN, Shi JF, Liu YP, Kan CX, Han F, Sun XD

MINIREVIEWS

- 1070 Multi-omics: Opportunities for research on mechanism of type 2 diabetes mellitus
Wang S, Yong H, He XD
- 1081 Role and function of granin proteins in diabetes mellitus
Herold Z, Doleschall M, Somogyi A

- 1093 Diabetes remission after bariatric surgery
Chumakova-Orin M, Vanetta C, Moris DP, Guerron AD

ORIGINAL ARTICLE**Basic Study**

- 1102 Decarboxylated osteocalcin, a possible drug for type 2 diabetes, triggers glucose uptake in MG63 cells
Jin S, Chang XC, Wen J, Yang J, Ao N, Zhang KY, Suo LN, Du J
- 1116 Expression and role of P-element-induced wimpy testis-interacting RNA in diabetic-retinopathy in mice
Yu Y, Ren KM, Chen XL

Observational Study

- 1131 Fasting biochemical hypoglycemia and related-factors in non-diabetic population: Kanagawa Investigation of Total Check-up Data from National Database-8
Tanaka K, Higuchi R, Mizusawa K, Nakamura T, Nakajima K

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Gong Su, MD, PhD, Chief Physician, Deputy Director, Center of Cardiology, Hangtian Central Hospital, Peking University, Beijing 100049, China. su_gong@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes (WJD, World J Diabetes)* is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJD* as 3.763; IF without journal self cites: 3.684; 5-year IF: 7.348; Journal Citation Indicator: 0.64□Ranking: 80 among 145 journals in endocrinology and metabolism; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Li-Li Wang; Production Department Director: Yu-Jie Ma; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

July 15, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Ejaculatory dysfunction in men with diabetes mellitus

Taymour Mostafa, Ibrahim A Abdel-Hamid

ORCID number: Taymour Mostafa 0000-0003-3627-0662; Ibrahim A Abdel-Hamid 0000-0002-0333-8723.

Author contributions: Mostafa T and Abdel-Hamid IA contributed equally to this work in all its aspects.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Andrology

Country/Territory of origin: Egypt

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Taymour Mostafa, Department of Andrology & Sexology, Faculty of Medicine, Cairo University, Cairo 11562, Egypt

Ibrahim A Abdel-Hamid, Department of Andrology, Mansoura Faculty of Medicine, Mansoura 35516, Egypt

Corresponding author: Taymour Mostafa, PhD, Professor, Department of Andrology & Sexology, Faculty of Medicine, Cairo University, Cairo 11562, Egypt. taymour1155@link.net

Abstract

Diabetes mellitus (DM) is a metabolic disorder that is characterized by elevated blood glucose levels due to absolute or relative insulin deficiency, in the background of β -cell dysfunction, insulin resistance, or both. Such chronic hyperglycemia is linked to long-term damage to blood vessels, nerves, and various organs. Currently, the worldwide burden of DM and its complications is in increase. Male sexual dysfunction is one of the famous complications of DM, including abnormal orgasmic/ejaculatory functions, desire/libido, and erection. Ejaculatory dysfunction encompasses several disorders related to DM and its complications, such as premature ejaculation, anejaculation (AE), delayed ejaculation, retrograde ejaculation (RE), ejaculatory pain, anesthetic ejaculation, decreased ejaculate volume, and decreased force of ejaculation. The problems linked to ejaculatory dysfunction may extend beyond the poor quality of life in diabetics as both AE and RE are alleged to alter the fertility potential of these patients. However, although both diabetes patients and their physicians are increasingly aware of diabetic ejaculatory dysfunction, this awareness still lags behind that of other diabetes complications. Therefore, all these disorders should be looked for thoroughly during the clinical evaluation of diabetic men. Besides, introducing the suitable option and/or maneuvers to treat these disorders should be tailored according to each case. This review aimed to explore the most important findings regarding ejaculatory dysfunction in diabetes from pre-clinical and clinical perspectives.

Key Words: Diabetes mellitus; Ejaculation; Anejaculation; Retrograde ejaculation; Semen

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Male sexual dysfunction is a famous complication of diabetes mellitus (DM),

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: January 30, 2021**Peer-review started:** January 30, 2021**First decision:** May 3, 2021**Revised:** May 6, 2021**Accepted:** June 15, 2021**Article in press:** June 15, 2021**Published online:** July 15, 2021**P-Reviewer:** Kamalanathan S**S-Editor:** Zhang H**L-Editor:** Filipodia**P-Editor:** Wang LL

including abnormal orgasmic/ejaculatory function, desire/libido, and erection. DM-related ejaculatory dysfunction encompasses several disorders such as premature ejaculation, anejaculation (AE), delayed ejaculation, retrograde ejaculation (RE), ejaculatory pain, anesthetic ejaculation, decreased ejaculate volume, and decreased force of ejaculation. The problems linked to ejaculatory dysfunction may lead to poor quality of life as both AE and RE are alleged to alter their fertility potential. All these disorders should be looked for thoroughly during the clinical evaluation of diabetic men.

Citation: Mostafa T, Abdel-Hamid IA. Ejaculatory dysfunction in men with diabetes mellitus. *World J Diabetes* 2021; 12(7): 954-974

URL: <https://www.wjgnet.com/1948-9358/full/v12/i7/954.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v12.i7.954>

INTRODUCTION

Ejaculation is a complex, coordinated sequence of mechanisms and reflexes compared to erection. It requires coordinated innervation of the sympathetic and parasympathetic systems in addition to somatic innervation. In essence, it is intermediated by a multifaceted neural control system including sensory receptors, afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers, and efferent pathways. Likewise, this process comprises complex neurochemical interplay between central serotonergic and dopaminergic neurons, with involvement of cholinergic, adrenergic, oxytocinergic, and gamma-aminobutyric acidergic neurons[1]. However, ejaculation entails two diverse sequential coordinated phases, seminal emission and ejaculation proper, each of them involving diverse anatomic structures[2].

The sympathetic nervous system is accountable for bladder neck closure and emission, whereas the somatic nervous system is accountable for the contraction of the pelvic muscles and the bulbourethral and ischiocavernosus muscles[3]. Additionally, the external urinary bladder sphincter as well as the perineal periurethral muscles are under somatic control[4]. Emission process is characterized by closure of the bladder neck and contraction of smooth muscles across the seminal tract aiming of propulsion of the ejaculate constituents into the posterior urethra where they are mixed with spermatozoa to form seminal fluid[5]. This phase is activated by augmented sexual arousal and the peripheral sex-related stimuli. The sympathetic centers, found within the intermediolateral and the intermediomedial cell columns in lamina VII of segments T₁₂-L₂, supply the smooth muscles of the male accessory glands, seminal tract, and urinary bladder neck[6]. Before emission, there are secretions from the distal epididymis, seminal vesicles (SVs), and the prostate supporting emission. Neural control of those secretions is mediated by the cholinergic post-ganglionic, sympathetic, and parasympathetic fibers, derived from the pelvic plexus[6-8]. The emission phase is under the cerebral control and can be affected by the physical or visual erotic stimulation[9].

The ejaculation proper phase follows emission and refers to the relaxation of the external urinary sphincter followed by repetitive contractions of the bulbospongiosus, ischiocavernosus, and the pelvic striated muscles leading to expulsion of seminal fluid out of the urethra[10]. Motor neurons controlling the pelvic and perineal striated muscles are situated in the ventral horn of segments S₂-S₄ in Onuf's nucleus[11]. Both emission and ejaculation proper occur in coherence to bring normal antegrade ejaculation. Although the precise trigger for the ejection phase is not yet known, it is believed that the filling of the posterior urethra urges the urethral-muscular reflex boosted by sensory inputs-somatosensory, visceral sensory, or proprioceptive-to the spinal control center might trigger the onset of ejection. Harmonization between autonomic and somatic neurons for emission as well as ejection is supposed to be controlled by a group of lumbar spinothalamic interneurons called "spinal ejaculation generator (SEG)"[12]. In rats, these interneurons are situated in lamina X and the medial part of lamina VII of the gray matter in the L₃-L₄[13]. In humans, neurohistologic data, in addition to the clinical observations, have established the existence of SEG in L₃-L₅ segments[14].

Exact knowledge on hormonal control of ejaculation is still lacking. Studies have shown an oxytocin surge during male sexual activity, peaking during or soon after ejaculation[15]. Additionally, oxytocin's contractile effect concerning the seminal tract in humans appears to be weaker than in the animal models[16]. Moreover, estrogens have been demonstrated to take part in the peripheral regulation of epididymal contractility[17]. Furthermore, prolactin was also noted to increase around orgasm with oxytocin suggesting that it may serve as a neuroendocrine reproductive reflex for peripheral reproductive organs[18,19]. Androgens are deeply elaborated in the ejaculation process[20]. The effects of androgens are not limited to the fact that the development of the epididymis, vas deferens, and SVs is dependent on androgens, but also, spinal nuclei elaborated in the control of ejaculation, such as the nucleus of the bulbocavernosus nerve, are androgen-dependent[21], as are the muscles of the pelvic floor[22,23]. However, the dynamic and complex interplay among androgens, growth factors, and genes in the ejaculatory process is less well understood.

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion and/or action[24]. The worldwide burden of DM and its complications are presently in an increase. DM is usually associated with long-term dysfunction of blood vessels, nerves, and several organs including the epididymis, vas deferens (VD), SV, prostate, and urethra[25-29]. Although both diabetes patients and their physicians are increasingly aware of diabetic ejaculatory dysfunction, this awareness still lags behind that of other diabetes complications. The problems linked to the ejaculatory dysfunction may extend beyond the poor quality of life in diabetics. Because anejaculation (AE) and retrograde ejaculation (RE) are believed to alter the fertility potential of patients[25,30]. Thus, the careful diagnosis and timely management of these cases together are of extreme importance. Therefore, this narrative review aims to explore the most important findings regarding ejaculatory dysfunction in diabetes from pre-clinical and clinical perspectives.

METHODS

We searched the PUBMED/MEDLINE, Scopus, Academic Search Complete database, Google Scholar, Cochrane Library, EMBASE, ProQuest, and CINAHL databases from inception to December 2020, for relevant studies. The literature search included these terms (with synonyms and closely related words): type 1 and type 2 diabetes mellitus; or hyperglycemia; or insulin resistance; and ejaculatory dysfunction; or premature ejaculation (PE); or delayed ejaculation (DE); or AE; or RE; or ejaculatory pain (EP); or anesthetic ejaculation; or spontaneous ejaculation (SE); or sexual dysfunction; or male sexual function; or epididymis; or VD; or SVs; or prostate; bladder neck; or urethra. The search was not limited by study design but restricted to English-language periodicals. Further studies were recognized by examining the reference lists of all retrieved articles.

ANIMAL STUDIES

In an attempt to understand the influence of DM on ejaculatory function, we have identified 18 studies (Table 1) reporting on the association between experimental DM and ejaculatory dysfunction. Generally, it seems that ejaculatory dysfunction after experimental DM is inexplicable because it ranges from PE, normal ejaculatory performance, to AE. Although the duration of the diabetic state seems to be the major determinant of the development of ejaculatory dysfunction, other factors such as dissimilar animal species and strains, with a diversity of metabolic pathways, different models for inducing DM, small experimental groups, nuances in laboratory technique that may affect the results, and selection of outcome measures of the ejaculatory function. Nonetheless, the following different observations were noted: (1) 3 studies showed no sexual performance difference between diabetic and control rats[31-33]; (2) prolonged ejaculation latency (EL) was reported in 9 studies suggesting DE[34-42]. Notably, in 1 study diabetic rats showed a significantly decreased amount of secretions stored in the seminal vesicle indicating that streptozotocin (STZ)-induced diabetic might affect the cholinergic nerve endings that are situated at the rich glandular epithelium[38]; (3) 0% ejaculations (rats did not achieve ejaculation) was noted in 4 reports suggesting AE[43-46]; and (4) reduced EL was reported in 2 reports suggesting PE[47,48]. These findings suggest not only that ejaculatory dysfunction in diabetic

Table 1 Ejaculatory behavior in diabetic animals

Ref.	Animal model	Effects observed on ejaculatory function	Type of treatment and response
Sach <i>et al</i> [31], 1982	STZ-induced diabetic rats	No sexual performance difference between diabetic and control rats.	
Clark[32], 1995	STZ-induced diabetic rats	No sexual performance difference between diabetic and control rats.	
Scarano <i>et al</i> [33], 2006	STZ-induced diabetic rats	No sexual performance differences in EL after 15 d.	
Steger <i>et al</i> [34], 1990	STZ-induced diabetic rats	Prolonged EL (DE or AE)	Delayed insulin replacement (4 wk) cannot prevent ejaculatory dysfunction.
Murray <i>et al</i> [35], 1992	Diabetic BB/WOR rats	Prolonged EL (DE or AE) after 28 wk	
McVary <i>et al</i> [36], 1997	Diabetic BB/WOR rats	Prolonged EL (DE or AE) after 40 wk, reduced number of ejaculations. No differences regarding serum testosterone, FSH, and LH.	
Ebiko <i>et al</i> [37], 2006	STZ-induced diabetic rats	Deteriorated spontaneous seminal emission after 5 wk. In 15 and 30 wk, occurrence of SSE was almost completely suppressed.	Early insulin replacement can prevent ejaculatory dysfunction.
Yonezawa <i>et al</i> [38], 2009	Streptozotocin (STZ)-induced diabetic rats	Deteriorated spontaneous seminal emission after 5 wk. Decreased ejaculated semen and decreased seminal vesicle fluid.	Early insulin replacement can prevent ejaculatory dysfunction. Once dysfunction occurs, insulin cannot restore it.
Suresh <i>et al</i> [39], 2012	STZ-induced diabetic rats	Prolonged EL suggesting DE. -Low serum testosterone.	Mucuna pruriens showed recovery of EL.
De <i>et al</i> [40], 2016	STZ-induced diabetic rats	Prolonged EL suggesting DE. -Low serum testosterone.	l-Norvaline (arginase inhibitor) reduced EL.
Shi <i>et al</i> [41], 2017	STZ-induced diabetic rats	Prolonged EL suggesting DE.	Lycium barbarum polysaccharide reduced EL.
Li <i>et al</i> [42], 2019	STZ-induced diabetic rats	Prolonged EL at 62 d suggesting DE.	No effect of vitexin (herb) on EL.
Lert-Amornpat <i>et al</i> [43], 2016	STZ-induced diabetic rats	Lack of copulatory behavior suggesting AE.	<i>Kaempferia parviflora</i> (herb) showed recovery of EL.
Fernández-Collazo <i>et al</i> [44], 1970	Rats with subtotal pancreatectomy	They did not AE.	
Hassan <i>et al</i> [45], 1993	STZ-induced diabetic rats	Rats exhibited AE in diabetics. -Low serum testosterone.	Sabeluzole treatment was beneficial to correct dysfunction.
Pontes <i>et al</i> [46], 2011	STZ-induced diabetic rats	Lack of the sperms ejaculated into the uterus. -Low serum testosterone.	Testosterone supplement did not restore ejaculatory function.
Ghaheri <i>et al</i> [47], 2018	STZ-induced diabetic rats	Shorten EL after 28 d suggesting PE.	Stevia Bertoni extract improved EL.
Minaz <i>et al</i> [48], 2019	STZ-induced diabetic rats	Shorten EL after 8 wk suggesting PE. - Low serum testosterone.	Inhibition of soluble epoxide hydrolase prolonged EL.

AE: Anejaculation; DE: Delayed ejaculation; EL: Ejaculation latency; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; PE: Premature ejaculation; STZ: Streptozotocin.

animals is variable but also may indicate that the dysfunction may occur during the early stage following experimental diabetes and becomes poorer as it progresses[34, 38]. Additionally, early insulin replacement had been demonstrated to prevent ejaculatory dysfunction suggesting that insulin may play a role in controlling of seminal emission[34,37,38]. However, once the dysfunction occurs; delayed insulin replacement cannot restore normal ejaculatory function suggesting that long-term exposure to the hyperglycemia may lead to an irreversible ejaculatory dysfunction[34, 38]. In this respect, it appears that insulin replacement may only delay rather than prevent changes in copulatory behavior[34].

The development of ejaculatory dysfunctions in animals is not limited to STZ-induced diabetic rats[34,37-40,43,45-48] but also have been demonstrated in STZ-induced diabetic mice[42,43], subtotal pancreatectomy-induced diabetic rats[44], and Bio Breeding Wistar Strain (BB/WOR) rats with spontaneous DM[35,36]. The major attributes of this latter strain (BB/WOR) are not only limited to the fact that its pathophysiology closely look like the development as well as the clinical features of type 1 diabetes in humans but also it lacks the artefactual end-organ changes seen with STZ such as angiopathy[36]. In other words, diabetic neuropathy is a prevailing feature of this model[49]. EL, the time of the first intromission until ejaculation, was the most frequently employed outcome measure to assess the ejaculatory function in these animal studies[34-36,39-43,47,48]. Other tools include spontaneous seminal emission test[37,38], measurement of seminal vesicle fluid[38], failure to recover spermatozoa in the female uterus[46], and numbers of ejaculations[36,43-45].

In the context of ejaculatory dysfunction associated with experimental DM, it would be of interest to review the potential effects of different therapeutic compounds to restore the ejaculatory function in STZ-induced diabetic mice. Nine studies were identified[39-43,45-48]. Animal studies have demonstrated that *Mucuna pruriens*[39], L-Norvaline (arginase inhibitor)[40], and Lycium barbarum polysaccharide[41] showed a reduction in the EL in those showing prolonged EL during the diabetic state. Additionally, both *Kaempferia parviflora*[43], and sabeluzole (benzothiazole derivative)[45], were found to be beneficial in correcting an ejaculatory condition. Moreover, Stevia Bertoni extracts and the soluble epoxide hydrolase inhibitor “trans-4-{4-[3-(4-trifluoromethoxyphenyl)-ureido] cyclohexyloxy} benzoic acid/t-TUCB”[47,48] showed prolongation of EL in those animals showing a reduction in EL. Unfortunately, both vitexin (bioactive flavonoids) and testosterone did not restore ejaculatory function in STZ-induced diabetic and mice, respectively. Finally, further experiments are needed to delineate better the effects of experimental diabetes on the ejaculatory function using a unified generally accepted easily measurable outcome measure.

ETIOPATHOGENESIS OF DIABETIC EJACULATORY DYSFUNCTION

Animal studies assessed the effects of experimental diabetes on the end-organs of a seminal emission (epididymis, VD, SV, prostate, bladder neck, and urethra) have revealed that hyperglycemia is capable of altering the contractility of these organs either by modulating neurotransmitters release or by modifying the basal tone of the smooth muscle layers[50-52]. Interference with the normal function of these organs may therefore include central or peripheral mechanisms. Besides, these diabetes-associated changes may have general pathophysiological interest since ejaculatory dysfunction such as PE, DE, AE; or RE has been proven to be one of the complications of DM[25,27,28]. Moreover, animal models can deliver an important method to assess neural circuitry and molecular and cellular pathways in an organized setting. The following summarizes the major observations regarding the effects of experimental diabetes on the end-organs of seminal emission to understand the pathogenesis of diabetes-associated ejaculatory dysfunction: (1) Chronically STZ-diabetic rats and mice showed degenerative changes in the sympathetic supply of the VD leading to a decreased reaction to stimulation of their noradrenergic nerves and a supersensitivity to exogenous noradrenaline[50-54]. These findings suggest that a significant proportion of animals may have developed sympathetic neuropathy that may explain the prolongation of EL, reduction of the numbers of ejaculations, and the occurrence of AE; (2) The paravertebral thoracic ganglion cells of spontaneously diabetic BB rats exhibited a decreased number of synapses and the postganglionic fibers demonstrated increased glycogenosomes, axonal sequestration, and reduced axonal size suggesting an axonopathy in sympathetic nerves[49,53]. Additionally, this model showed a peripheral neuropathic change in both the hypogastric and motor pudendal nerve fibers suggesting that diabetic neuropathy is not only disturbed the emission phase but also may disrupt the ejection phase of the ejaculatory process[36]; (3) Reactive oxygen species (ROS) may be accountable for impaired sympathetic neurotransmission and the abnormal function of diabetic vas deferens in STZ-diabetic rats[54,55]; (4) There is evidence to suggest the presence of Ca channel hyperactivity in the smooth muscle of VD of STZ-induced diabetic rats possibly due to increased phosphatidylinositol turnover mediated by alpha 1-adrenoceptors[56,57]. These findings may reduce EL and explain the occurrence of PE; (5) Noradrenaline is the principal excitatory neurotransmitter in the internal urethral sphincter and augments closure of the bladder neck during ejaculation[58,59]. By principle, the combination of long-term

diabetic sympathetic neuropathy in animals[37,38,49] and external urethral sphincter relaxation dysfunction[60] may result in RE; (6) It has been demonstrated that long-term diabetes is associated with changes in serotonergic transmission in the rat brain including changes in several types of 5-HT receptors[61,62]. Theoretically, 3, 5-HT receptor subtypes (5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C}) were assumed to mediate 5-HT's modulating activity on the ejaculation process. PE is associated with decreased neurotransmission of serotonin, 5-HT_{2C} receptor hyposensitivity, and 5-HT_{1A} receptor hypersensitivity[63]. Accordingly, ejaculatory dysfunction due to changes in serotonergic transmission among diabetic animals could be anticipated; (7) There is adequate evidence to suggest that experimental diabetes in different animal models (STZ rats, spontaneously diabetic BB rats, BB/WOR diabetic rats, and spontaneously diabetic Torii rats) is associated with low testosterone levels[64-70]. The pathogenesis of hypogonadism in diabetic animal models may include impaired hypothalamic or pituitary signaling[34,71,72], deficiency of gonadotropic hormones, or blockade of their actions[73,74], and/or primary Leydig cell defect in steroidogenesis due to lack of stimulating effect of insulin[74-76]. In the light of the foregoing, it might be assumed that there is a link between low testosterone levels and ejaculatory dysfunction. However, it has been shown that testosterone supplement is not able to bring back ejaculatory function in induced diabetic rats[46,77] suggesting that the deficiency of testosterone was not related directly to the diabetes-induced ejaculatory dysfunction in this experimental model. Although expression of androgen receptors are demonstrated at different levels of the ejaculatory process such as the medial preoptic area of the hypothalamus[78], smooth muscles of the male genital tract[79], and in the spinal nucleus of the bulbocavernosus muscle[80], it is thought that testosterone plays a much superior role in libido than the ejaculatory process and the physiological capacity for ejaculation is less sensitive to testosterone reduction than that for the desire[81,82]. In support of this notion, it has been shown that testosterone levels as low as 0.2 ng/mL, can support ejaculatory behavior in rats[83]; (8) It is possible that diabetic ejaculatory dysfunction might be a reflection of decreased sexual desire[36, 48]. Although the classic description of diabetic erectile dysfunction showed preserved desire[84], it has been shown that sexual desire (mount frequency) is notably decreased in diabetic rats[34,45,85-87], but this possibility was unlikely because of the absence of improved ejaculation behavior among diabetic rats after testosterone therapy despite the improvement of their libido (mount behavior)[77]; and (9) Lastly other factors that may participate in the pathogenesis of ejaculatory dysfunction in experimental diabetes may include decreased body and reproductive organs weight [45,77]. However, the relationship between these variables and diabetic ejaculatory dysfunction remains incompletely understood.

Ejaculatory dysfunctions are established complications found with variable prevalence in men with diabetes. There is also a substantial contribution of human studies to the pathogenesis of diabetic ejaculatory dysfunction. The factors that have been postulated to influence the development of ejaculatory dysfunctions in DM are summarized (Tables 2 and 3). However, there are limited data regarding the weight of each mechanism in participating in the pathogenesis of different ejaculatory dysfunctions in diabetes patients.

DIABETES-RELATED EJACULATORY DYSFUNCTIONS

Ejaculatory dysfunctions encompass several disorders related to DM and its complications, such as PE, DE, AE, RE, ejaculatory pain, anesthetic ejaculation, decreased ejaculate volume, and decreased force of ejaculation. Up to 40% of men with diabetes may complain of ejaculatory dysfunction[99]. Of these PE, DE, AE, and RE are the most common and the focus of this discussion[100-113].

PE

There is contradictory evidence concerning the prevalence of PE in diabetics, with one study reporting increased PE prevalence in diabetic men compared to healthy controls (78.8% vs 47.5%, $P = 0.001$)[92]. On the other hand, a study by the Italian Society of Andrology pointed out to a protecting effect of diabetes on PE (6.2% vs 8.4%, adjusted odds ratio = 0.6, $P = 0.001$)[114]. This low prevalence was endorsed to delayed emission caused by diabetic sympathetic neuropathy of nerve fibers innervating the organs of emission (VD, SV, prostate). However, with the well-known relation between erectile dysfunction (ED) and PE that recognizes ED as the significant comorbidity of PE[115] and a higher prevalence of ED among diabetics, we could

Table 2 Possible pathophysiological mechanisms underlying ejaculatory dysfunctions in diabetes mellitus (animal studies)

Ref.	Postulated mechanisms	Possible ejaculatory dysfunction
McVary <i>et al</i> [36], Yagihashi <i>et al</i> [49]	Pathologic changes in the nerve supply of seminal tract due to accumulation of AGE increased ROS (sympathetic neuropathy)	Prolongation of EL
Tomlinson <i>et al</i> [50], Longhurst <i>et al</i> [51]	Decreased number of synapses in thoracic ganglia	Reduction of the numbers of ejaculations
Kaschube <i>et al</i> [52], Kamata <i>et al</i> [53]	Axonopathy in postganglionic sympathetic fibers	Disturbed the emission phase
Güneş <i>et al</i> [54], Tsounapi <i>et al</i> [55]	Neuropathic changes in hypogastric nerve and motor pudendal nerve fibers	Disruption of the ejection phase
Tomlinson <i>et al</i> [50], Longhurst <i>et al</i> [51], Kaschube <i>et al</i> [52], Kamata <i>et al</i> [53], Güneş <i>et al</i> [54]	Hypersensitivity (supersensitivity) of seminal tract smooth muscles to exogenous noradrenaline	Reduction of EL
Sakai <i>et al</i> [56], Sakai <i>et al</i> [57]	Hyperactivity of Ca channels in smooth muscles	Reduction of EL
Ebiko <i>et al</i> [37], Yonezawa <i>et al</i> [38], Yagihashi <i>et al</i> [49], Torimoto <i>et al</i> [60]	Sympathetic neuropathy and external urethral sphincter relaxation dysfunction	Disruption of bladder neck closure Disruption of AE
Sandrini <i>et al</i> [61], Abraham <i>et al</i> [62]	Changes in serotonergic transmission	Reduction or prolongation of EL
Seethalakshmi <i>et al</i> [71], Wolfe <i>et al</i> [72]	Impaired hypothalamic or pituitary signaling	Decreased sexual performance
Oksanen <i>et al</i> [73], Sudha <i>et al</i> [74]	Deficiency of gonadotropic hormones or blockade of their actions	Decreased sexual performance
Ballester <i>et al</i> [75], Neirijnck <i>et al</i> [76]	Decrease in number and function of Leydig cells	Decreased sexual performance
Neirijnck <i>et al</i> [76]	Defective testicular steroidogenesis	Decreased sexual performance
Kühn-Velten <i>et al</i> [64], Anderson <i>et al</i> [65], Ricci <i>et al</i> [66], Murray <i>et al</i> [67], Cameron <i>et al</i> [68], Ohta <i>et al</i> [69], Nakane <i>et al</i> [70]	Reduced serum levels of LH and testosterone (T)	Decreased sexual performance
McVary <i>et al</i> [36], Minaz <i>et al</i> [48], Steger <i>et al</i> [85], Al-Roujayee <i>et al</i> [86], Kashif <i>et al</i> [87]	Reduced libido	Decreased sexual performance, decreased mount frequency, and reduced EL
Hassan <i>et al</i> [45], Steger <i>et al</i> [77]	Reduced reproductive organ weight	Exact Effects on ejaculation still unknown

AGE: Advanced glycation end products; Ca: Calcium; DE: Delayed ejaculation; EL: Ejaculation latency; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; PE: Premature ejaculation; ROS: Reactive oxygen species; STZ: Streptozotocin; T: Testosterone.

speculate that diabetes might be considered a risk factor for PE. Anyway, most of the studies showed comparable prevalence between diabetic and non-diabetic persons[90, 91,95,96]. Theoretically, diabetes-related PE is recognized to have a multi-factorial etiology (Tables 2 and 3). The lack of a significant difference in the prevalence of PE among men with/without diabetes might be attributed to socio-demographic factors, a multiplicity of different tools for measurement of PE such as self-reported PE, PE diagnostic tool (PEDT) score, self-reported, and stopwatch-recorded intravaginal ejaculation latency time (IELT) or to the presumed balance between the protective and detrimental factors inside the diabetes patients. Therefore, the true prevalence of PE in DM has not been firmly established. However, the PE subjects diagnosed with PEDT score or stopwatch IELT showed significant prevalence of diabetes[88,116] suggesting that DM is an important etiologic factor in acquired PE. Studies assessing whether PE in DM can be related to glycometabolic control and associated morbidities have also produced mixed results. While El-Sakka[91] and Malavige *et al*[93] have demonstrated that elongated duration of diabetes, poor metabolic control, and presence of cardiovascular disease are linked to increased risk of PE in type 2 DM, Other studies have found no such evidence in type 2 DM[92,97]. Additionally, in the subgroup of type 1 DM patients assessed for glucose variability, the PEDT score was associated with low blood glucose indices ($r = 0.43$; $P = 0.01$), but not with a standard deviation of blood glucose ($r = 0.1$, $P = 0.6$), mean amplitude of glycemic excursions ($r = -0.1$; $P = 0.4$), or high blood glucose indices ($r = 0.1$; $P = 0.6$) suggesting a link between glycemic excursions and PE[96]. This association between hypoglycemia and PE might be linked to increased adrenergic activity[117] or reduced serotonergic activity[118]. Moreover, PE is known to be associated with diabetes-related ED as shown in different studies[91-93,97]. Likewise, one study suggests that 95% of Type 2 diabetes patients

Table 3 Possible pathophysiological mechanisms underlying ejaculatory dysfunctions in diabetes mellitus (human studies)

Ref.	Possible cause	Outcome
Premature ejaculation		
Culha <i>et al</i> [88]	Anxiety	Among PE patients with DM, 15% had anxiety
Culha <i>et al</i> [88], Khan <i>et al</i> [89]	Depression	Among PE patients with DM, 16.9% had depression
		Depression score Significantly higher among diabetic-related PE patients
Khan <i>et al</i> [89], Malavige <i>et al</i> [90]	Genetic and racial factors	Long tri-nucleotide repeats of the androgen receptor are related to the lowest IELT (PE)
		Asian men reported higher diabetic PE than European counterparts
El-Sakka[91]	Diabetic condition, duration of MD	> 10 yr of diabetes were 2.7 times as likely to report diabetic-related PE
	Poor glycemic control	Poor glycemic control were 9.6 times as likely to report PE
El-Sakka[91], Majzoub <i>et al</i> [92]	Having diabetic-related -erectile dysfunction (ED) and Cardiovascular diseases	Significant association between PE and cardiovascular diseases
Malavige <i>et al</i> [93], Malavige <i>et al</i> [90]		ED showed a significantly higher incidence of PE
Olamoyegun <i>et al</i> [94]		ED was strongly associated with PE odds ratio = 4.4
El-Sakka[91]	Having diabetic -related neuropathy	It is not associated with PE
Khan <i>et al</i> [89]	Total serum testosterone	Significantly higher among type 2 diabetic-related PE patients
Owiredu <i>et al</i> [95]		It correlates negatively with short IELT among type 2 DM
Bellastella <i>et al</i> [96]		No significant difference in type 1 diabetes
Delayed ejaculation and anejaculation		
Corona <i>et al</i> [97]	Depression	Severe depressive symptoms are associated with ejaculatory problems in DM
Ellenberg <i>et al</i> [25], La Vignera <i>et al</i> [27], Dinulovic <i>et al</i> [98]	Progressive autonomic neuropathy of the sympathetic nerves	Denervation leads to weak or loss of VD and SV peristaltic movements
Dunsmuir <i>et al</i> [99], Condorelli <i>et al</i> [100]		Abnormal inflammatory responses lead to alteration of the VD and SV peristaltic movements
La Vignera <i>et al</i> [101], Pop-Busui <i>et al</i> [102]		Delayed /poor emission Absent emission
Haddad <i>et al</i> [26], Culver <i>et al</i> [103]	Calcification of vas deferens and seminal vesicles	Loss of their ability to contract as the smooth muscle is replaced by fibrotic, calcified tissue
Tsuno <i>et al</i> [104]		Delayed/poor emission
Hylmarova <i>et al</i> [29], Corona <i>et al</i> [81]	Hypogonadism	No association between serum testosterone levels and ejaculation time in men self-reporting DE including diabetic patients
Paduch <i>et al</i> [82], Gianatti <i>et al</i> [105]		
Morgentaler <i>et al</i> [106]		T replacement is not associated with improvement in DE or AE
Burke <i>et al</i> [107], Corona <i>et al</i> [108]	Low sexual desire	DM is significantly associated with low sexual desire
Corona <i>et al</i> [109]		DE and AE are associated with low sexual desire
Retrograde ejaculation		
Klebanow <i>et al</i> [110]	Diabetic neuropathy (T10-L3)	Intact vasal and seminal vesicle contraction but incomplete simultaneous bladder neck closure leads to partial RE
Greene <i>et al</i> [111]		Intact vasal and seminal vesicle contraction and simultaneous complete lack of bladder neck closure leads to complete RE

Koyanagi[112]	External urethral sphincter relaxation dysfunction (triple parasympathetic-sympathetic-somatic innervation)	Lack of active external urethral sphincter relaxation leads to disruption of antegrade ejaculation
Cao <i>et al</i> [113]		

AE: Anejaculation; DE: Delayed ejaculation; DM: Diabetes Mellitus; EL: Ejaculation latency; ED: Erectile dysfunction; PE: Premature ejaculation; SV: Seminal vesicle; VD: Vas deferens.

with PE also reported ED[91] indicating that ED is the principal risk factor of PE in type 2 DM. A vicious cycle probably exists between ED and PE with each condition being deteriorated by the other[93]. However, Culha *et al*[88] disputed these findings and have shown that simultaneously occurring different etiologic factors may be responsible for the development of DM-related PE. These factors include ED (20.75%), chronic prostatitis (18.87%), depression (16.98%), anxiety (15.09%), FSH-LH abnormality (7.55%), hyperprolactinemia (7.55%), and hyperthyroidism (1.89%). These latter findings still await confirmation.

According to the consensus of the International Society for Sexual Medicine, acquired PE (*e.g.*, diabetes-related PE) is an ejaculation that always or nearly always occurs before or within about 3 min of vaginal penetration or, a significant and bothersome reduction in the latency time, associated with the incapability to delay ejaculation on all/nearly all vaginal penetrations, and negative personal consequences, as; distress, bother, frustration and/or avoidance of sexual intimacy[119]. Evaluation of diabetes-related PE includes a clinical history and careful physical examination focusing on all related symptoms, signs, and risk factors. A list of assessment steps that could be helpful in evaluating DM-related ejaculatory dysfunction is presented (Table 4). The most important dimensions in history taking include assessment of self-estimated IELT, subjective perceived control over ejaculation, existed distress by the condition, and the existence of an interpersonal difficulty owing to PE. Routine laboratory tests or neuro-physiological tests should merely directed by precise findings from either the history taking or physical examination[120].

In principle, scarce data are assessing the treatment of DM-related PE. Additionally, one should know that DM-related PE may be a heterogeneous group of patients. Hence, it is important to diagnose any associated comorbidity such as ED, depression, prostatitis, or hyperthyroidism as they should be treated first or at the same time as PE [120]. Therefore, the treatment may involve numerous interventions as per the kind of mechanism that would cause such condition: (1) The initial management for PE is controlling the patient's blood glucose that in some cases may allow recover the normal ejaculatory function[91,93]; (2) Amelioration of glycemic variability would improve PE in type 1 diabetes patients[96]; (3) In cases of concomitant ED and PE, ED should receive phosphodiesterase type 5 inhibitors before, or at least at the same time as, PE[91,93,94]. The efficacy of the combined use of phosphodiesterase type 5 inhibitors and dapoxetine in males with comorbid PE and ED are supported by some studies[121-123]; (4) DM-related PE patients had a worse response to 30-60 mg oral dapoxetine treatment compared to non-diabetic PE patients. Poor treatment outcomes in diabetes patients may be attributed to DM-associated complications[123]; and (5) Various behavioral techniques (such as 'squeeze' technique or 'stop-start' program) may be beneficial in those associated with psychological factors or those patients uncomfortable with pharmacological therapy. However, the long-term success of these maneuvers is limited[120].

DE and AE

DE (also termed retarded ejaculation, inhibited ejaculation (IE), inadequate ejaculation, male orgasmic disorder, or primary impotentia ejaculationis,) was used to describe "a marked delay in or inability to achieve ejaculation" [124]. Current diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, defines DE as either a marked delay in or a marked infrequency or absence of ejaculation on 75% to 100% of occasions for at least 6 mo of partnered sexual activity without the individual desiring delay and causing significant distress to the individual[125]. Therefore, the terminology DE aimed to describe all ejaculatory disorders that lead to a delay or absence of ejaculation (AE)[1]. Furthermore, the severity of DE was classified according to Kaplan criteria into mild and moderate forms and the most severe ones (AE or severe DE)[126]. For these reasons, both DE and AE will be discussed together in this section.

Overall, DE is the rarest and the least understood male sexual dysfunction. Its incidence in the general population rarely exceeds 3% [127,128]. There have been few

Table 4 Assessment steps in the evaluation of diabetes mellitus-related ejaculatory dysfunctions**History**

Asking about the period from vaginal intromission to ejaculation (intravaginal ejaculatory latency time).

Is the patient unable to advance his ejaculatory response?

Is the patient or his partner distressed or bothered by the situation?

Is the symptom occurring since the first sexual experience or occurring after a period of normal ejaculatory performance?

Onset and duration of the symptom.

Is the symptom occurring on every/almost every attempt and with every partner?

Presence or absence of premonitory ejaculatory sensation.

The duration of thrusting before the suspension of intercourse.

Reasons for delay of intercourse (*e.g.*, fatigue, loss of erection, a sense of ejaculatory futility, or partner request).

Presence of post-coital self- or partner-assisted masturbation.

Psychogenic anejaculation/anorgasmia can be suspected when there is a history of nocturnal emission.

Patient's ability to get an erection, relax, sustain, and heighten sexual arousal.

Exclude anorgasmia by asking about lack of orgasm.

Whether orgasm is present but there is a lack of external ejaculation that may indicate retrograde ejaculate.

Feeling before ejaculation/orgasm: The inadequate combination of "friction and fantasy" may exacerbate DE.

Intercourse frequency.

Presence of other sexual dysfunctions such as ED (ability to initiate or maintain an erection), low libido.

Other symptoms of hypogonadism (such as lack of energy, depressed mood).

Masturbation habits

The life events/circumstances related to the complaint.

Sexual communication abilities.

Paraphilic inclinations/interests (may be related to DE and anejaculation).

Cultural or religious beliefs (if any).

History of a psychiatric disorder (may be the etiologic factor).

History of previous treatment for this symptom.

History of neurologic disorders, spinal cord injury, medical diseases, trauma, abdominal/pelvic operations, drug intake, or pelvic radiotherapy.

History of pelvic or testicular pain (may indicate inflammation).

History of dysuria, burning micturition, or any urinary symptom (indicate inflammation).

Clinical examination

Signs of diabetic complications and co-morbidities.

Signs of hypogonadism.

Rule out systemic disorders that contribute to ejaculation dysfunction as neurological impairment, endocrine/ urological diseases.

Examination for secondary sexual characteristics, penile and testicular abnormalities.

Examination of the epididymis, and vas deferens on each side.

PR examination to determine the prostate size, anal sphincter tone, and quality of the bulbocavernosus reflex.

The cremasteric reflex: measures intact L1-2 spinal segments, also mediating emission and psychogenic erection.

Perineal reflexes (bulbocavernosus and anal reflex) mediated by sacral segments, also mediating reflex erection (for intact S2-4 pathway).

Examination of pinprick and temperature sensations in the saddle area (perineal) and glans penis for healthy sacral cord segments.

Inability to feel testicular squeeze: measures the integrity of T11 to T12 spinal nerves *via* the sympathetic nervous system.

Examination of lower abdominal cutaneous reflex: measures intact Th11-12.

Penile biothesiometry.

Investigations

Blood levels of glucose, HbA1c, serum testosterone, thyrotropin, and prolactin to exclude other endocrine disorders.

Post-masturbation first-void urine if we suspect retrograde ejaculation to search for spermatozoa and fructose content to confirm retrograde ejaculate

Microbiological examination of expressed prostatic secretion and urine to verify or exclude associated genital infections.

Urine cytology to exclude bladder cancer

Serum prostate-specific antigen to exclude prostate cancer

Neurophysiologic investigations (bulbocavernosus evoked response and dorsal nerve somatosensory evoked-potentials): If there is clinical evidence of neurologic lesions. These tests are little used in clinical practice and usually do not affect management.

Trans-rectal ultrasound examination if we suspect ejaculatory duct obstruction, prostatic or seminal vesicle abnormalities or stones.

CT or MRI scans to assess pelvic anatomy if we suspect major pelvic lesions.

CT: Computed tomography; MRI: Magnetic resonance imaging.

attempts to study the prevalence of DE and AE in DM. While one study showed 0% prevalence among a series of 54 diabetes patients[129], another research demonstrated self-reported absent ejaculation and DE in 7.2 % and 0.36 % respectively among a total series of 276 diabetes patients[130]. However, sporadic cases were reported in literature either in the context of fertility evaluation[110,131] or as a sexual complaint [132]. It is thought that several pathophysiological factors may contribute to the development of DE and AE such as depression, progressive autonomic neuropathy, calcification of VD and SV, hypogonadism, or low sexual desire (Table 3).

Unfortunately, careful history is still the key there is no test to diagnose DE/AE [133]. It starts by excluding RE, genital tract obstruction, anorgasmia, and other sexual dysfunctions that may be misdiagnosed as DE/AE, such as ED, a subtly decreased libido, ejaculatory pain, the partner's sexual dysfunction, sexual orientation conflicts, or paraphilic inclinations/interests (Table 4). A focused psychosexual evaluation is critical and typically begins by differentiating whether the complaint concerns DE/AE, the sensation of orgasm, or both. Attention should be given to identifying reversible factors such as poor glycemic control, hypogonadism low sexual desire, psychological factors, and genital infections. A focused clinical examination, laboratory tests, as well as radiologic imaging may help to diagnose these risk factors (Table 4). Sometimes the diagnosis of those risk factor(s) unfolds over time many clinical visits[134].

In this context, defining solid approaches for the treatment of DM-related DE/AE is difficult for a condition that the literature is restricted to case reports, case series, or small studies. It is assumed that intensive glycemic control may reduce the prevalence of diabetic autonomic dysfunction and might slow the deterioration of DM-related DE/AE; unfortunately, no article studying this effect has been published. If organic and iatrogenic reasons have been let off in DM-related DE/AE behavioral therapy may be considered[1]. Several drugs are recognized for the possible use in DE/AE. Those agents include; testosterone, amantadine, cyproheptadine, cabergoline, bupropion, yohimbine, buspirone, bethanechol, and others. Yet, no drug was approved for this indication[125]. Testosterone replacement therapy may be an appropriate option for DM-related DE/AE with decreased testosterone levels. However, in a clinical trial, in which diabetes is not an exclusion criterion, Paduch *et al*[82] reported that treatment of testosterone-deficient DE patients with a 2% solution of testosterone is not linked to improved perceived delay of ejaculation suggesting that testosterone deficiency is not the sole contributor to DE. Mechanistically, diabetic autonomic neuropathy is an important factor in the development of DM-related DE/AE that may affect neural systems at all levels of emission and ejection. Once diabetic autonomic neuropathy becomes clinically evident, there is no treatment to reverse it[135]. In the most severe cases, there may be a total lack of seminal emission leading to male infertility. If infertility is an issue, several approaches can be employed: (1) Assisted ejaculation by penile vibratory stimulation (PVS) is an option for sperm retrieval[136] because it is noninvasive and inexpensive[137]. However, DM patients frequently fail to obtain sperms by this method because it requires intact lumbosacral pathways[136,137]; (2) In cases in whom PVS fails, electroejaculation (EEJ) may be effective to retrieve spermatozoa[99,138]; and (3) If these procedures fail, surgical sperm retrieval can be tried through VD aspiration[139], percutaneous epididymal sperm aspiration (PESA) [140], or testicular sperm extraction (TESA)[141]. Using spermatozoa obtained by any of these procedures and utilizing intracytoplasmic sperm injection (ICSI), one can

attain clinical pregnancy and live birth rates in DM-related AE. However, the fertilization rate and high-quality embryo rate in diabetic PE patients are lower than in non-diabetic PE patients[140].

RE

RE is unique in that it is almost exclusively organic in origin. Despite being a common type of ejaculatory dysfunction, it is responsible for only 0.3%-2% of infertility[142, 143]. Specifically, young men with type 1 diabetes have a higher incidence of ejaculatory dysfunction estimated to be 5%-18% of cases due to diabetic neuropathy, which has been shown to cause male infertility[29,144,145].

RE is an ejaculation that is deposited into the posterior urethra but propelled backward into the urinary bladder. In the normal state, the bladder neck closes with high pressure under the sympathetic control during orgasm and the seminal bolus takes the route of least resistance, being antegrade. Diabetic neuropathy can interfere with the sympathetic fibers that provide for normal high-pressure bladder neck closure, causing a comparatively low-pressure route into the urinary bladder for semen[146].

Impairment of sympathetic innervation of the urinary bladder neck was supposed to be a cause of diabetic RE. Ibragimov *et al*[147] used the liquid profilometric technique to examine 3 groups of men: 8 patients with RE; 5 patients with DM without ejaculatory disorders; and 7 healthy subjects. Diabetic RE patients showed no elevation of the intraureteral pressure in the area of the inner sphincter of the urinary bladder, which evidenced its atony. In health the elevation of vesical pressure is usually accompanied by increased ureteral resistance, thus maintaining the stability of the positive pressure gradient and preventing the escape of urine. Correlation analysis revealed alterations of the interrelations between both intravesical and sphincter pressures in diabetes patients evidencing the disorders of somatic innervation of the outer ureteral sphincter being more pronounced in these patients.

DIAGNOSIS

RE can be partial or complete and the diagnosis is frequently suggested by the patient's report of cloudy urine following orgasm confirmed by a post-ejaculatory urine analysis that reveals sperm, seminal fluid, or fructose[148]. McMahon[149] endorsed that the post-orgasmic urine should be centrifuged and visualizing of 10-15 sperm/high-power field could confirm RE diagnosis whereas Fedder *et al*[150] defined RE as > 1 million sperms in a post-ejaculatory urine sample.

TREATMENT STRATEGIES

Infertility is usually the main concern in RE patients as the combination of dry orgasm and infertility makes the condition upsetting to the patient and his partner[151]. Therefore, many lines of therapeutic approaches were advocated, either medical or surgical, with limited success rates.

Medical treatment

It is based either on increasing the sympathetic tone of the urinary bladder or on decreasing the parasympathetic activity but the onset of side effects and the lack of response should be considered. Several treatments were proposed with varied results [152-161] (Table 5).

Endourethral collagen injection

Kurbatov *et al*[145] analyzed the long-term outcome of endourethral injection of volume-forming material (VFM) of collagen type 2 into the bladder neck submucosa in 23 patients with RE secondary to type 1 DM with complete RE refractory to imipramine. These patients were randomized with a 1: 1 ratio into 2 groups; group A (endourethral collagen type 2 injection) and group B (endourethral saline water injection). This technique included an endoscopic injection of VFM such as collagen into bladder neck submucosa. In group A, significant differences from baseline to 12 mo were detected relative to antegrade volume (mean difference: 0.71 mL), antegrade count (mean difference: 45.6 million/mL), antegrade total sperm motility (mean difference: 15.4%), and antegrade progressive sperm motility (mean difference: 8.4%).

Table 5 Studies involving medical treatment for reversal of diabetic retrograde ejaculation

Ref.	Dosage	Ejaculation after	n	No. of successes	Ejaculate volume (ml)	Sperm count (10 ⁶ /m)	Sperm motility (%)
Brompheniramine							
Andaloro <i>et al</i> [152]	16 mg/d p.o.	12 h	1	1	Unclear	Unclear	Unclear
Budd[153]	16 mg/d p.o.	3 d	1	1	Unclear	Unclear	Unclear
Chlorpheniramine + phenylpropanalamine							
Stewart <i>et al</i> [154]	50 mg/d p.o.	Unclear	1	1	4.5	Normal	Normal
Ephedrine							
Gilja <i>et al</i> [155]	50 mg/d p.o.	4 wk	17	3	Unclear	Unclear	Unclear
Arafa <i>et al</i> [156]	120 mg twice/d	14 d	23	11	Unclear	Unclear	Unclear
Shoshany <i>et al</i> [157]	60 mg/6 h the day before test + 2 doses on test day	At the test	6	4	1.5	Unclear	17.8
Imipramine							
Brooks <i>et al</i> [158]	75 mg/d p.o.	1 wk	2	2	3	1.72	33
Okada <i>et al</i> [159]	25-150 mg/d	Unclear	7	3	Unclear	Unclear	Unclear
Gilja <i>et al</i> [155]	75 mg/d p.o.	4 wk	14	2	Unclear	Unclear	Unclear
Eppel <i>et al</i> [160]	50 mg/d p.o.	5 d	3	3	8	20	50
Arafa <i>et al</i> [156]	50 mg/d p.o.	14 d	23	10	Unclear	Unclear	Unclear
Imramine + pseudoephedrine							
Arafa <i>et al</i> [156]	50 + 120 mg/d	14 d	23	16	Unclear	Unclear	Unclear
Amoxapine							
Hibi <i>et al</i> [161]	50 mg/d	1 mo	1	1	0.2	213	53

It was concluded that correcting RE in type 1 DM patients could be accomplished with the endourethral injection of collagen type 2.

SPERM RETRIEVAL

Beyond using standard sperm retrieval techniques such as; TESE and PESA, 3 methods of sperm retrieval were recognized for managing infertility in RE patients. These techniques include; centrifugation and resuspension of post-ejaculatory urine specimens, the Hotchkiss (or modified Hotchkiss) technique, as well as ejaculation on a full urinary bladder.

Centrifugation and resuspension: To improve the conditions for the sperm, the patient is asked to either increase their fluid intake or to take sodium bicarbonate to dilute or alkalyze the urine. A post-orgasmic urine sample is collected by either introducing a catheter or spontaneous voiding. This sample is centrifuged and suspended in a medium such as bovine serum albumin, human serum albumin, Earle's/Hank's, phosphate-buffered medium. The resultant modified sperm mixture can be used in assisted reproductive techniques (ART) (Table 6)[162-165]. In their meta-analysis in couples with the male partner with RE, Jefferys *et al*[142] reported a 15% pregnancy rate/cycle (0%-100%) after using the centrifugation and resuspension method.

Hotchkiss method: It involves emptying the urinary bladder before ejaculation by a catheter, washing out and instilling a small quantity of lactated Ringers to improve the ambient conditions of the bladder. The patient then ejaculates and the semen is retrieved by catheterization or voiding[166].

Modified Hotchkiss method: It involves a variance in the instillation medium. Pregnancy rates were 24%/cycle (0%-100%)[142]. Philippon *et al*[167] reported the largest series of births using frozen-thawed sperms retrieved from post-ejaculatory urine by a this technique that allows for successful association with sperm cryopreser-

Table 6 Semen parameters of studies recovering sperms from alkalinized urine in diabetic premature ejaculation patients

Ref.	Medium installed	Post-masturbatory retrieval	No. of patients	Total sperm count (10 ⁶)	Total sperm motility (%)	Pregnancies
Brassco <i>et al</i> [163]	NaHCO ₃ 4 g	Voiding	3	91	28	3
Templeton <i>et al</i> [162]	NaHCO ₃	Voiding	1	Unclear	2-21	0
Shangold <i>et al</i> [164]	NaHCO ₃ 1.6 g	Voiding	1	30-240	0	5

vation, leading to efficient management of couples with refractory RE with an average live birth rate/transfer of 28%.

Ejaculation on a full bladder: The patient is encouraged to ejaculate on a full urinary bladder and semen is suspended in Baker's buffer [162].

EEJ

EEJ has been used to a restricted degree in diabetic men who have developed ejaculatory failure as a consequence of diabetic neuropathy. Gerig *et al* [131] described the experience of 2 male fertility programs using EEJ in managing men with ejaculatory failure secondary to DM. Overall, 29 EEJ procedures were performed in seven diabetic men with ejaculatory failure. Following EEJ, retrograde semen specimens retrieved from the urinary bladder contained a mean of 3444.5 million sperm (range 269.2-4996 million), mean sperm motility was 4% (range 0%-11%). Semen specimens were used for intrauterine insemination. It was concluded that EEJ can be successfully used to retrieve sperms from men with ejaculatory failure due to DM. That procedure requires general anesthesia, and the pregnancy rates after intrauterine insemination with the processed sperm were low. Therefore, AET could offer a practicable alternate, yielding higher success rates.

ICSI

ICSI-ART can greatly reduce the impact of sperm factors of infertility [167]. In cases of diabetic RE, TESA is combined with ICSI to treat infertility. Liu *et al* [168] assessed the effect of TESA-ICSI on first cycle ICSI-embryo transfer for type 2 diabetic patients in 1219 azoospermic patients or RE who were treated with TESA-ICSI classified into 2 groups; type 2 DM group ($n = 54$) and non-diabetic controls ($n = 1165$). There were no significant differences in clinical pregnancy, implantation, normal fertilization, or cleavage rates between these groups.

CONCLUSION

Ejaculatory dysfunction encompasses several disorders related to DM and its complications, such as PE, DE, AE, RE, ejaculatory pain, anesthetic ejaculation, decreased ejaculate volume, and decreased force of ejaculation. All these disorders should be looked for thoroughly during the clinical evaluation of diabetic men. Besides, introducing the suitable option and/or maneuvers to treat these disorders should be tailored according to each case.

REFERENCES

- Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, Ahn TY. Disorders of orgasm and ejaculation in men. *J Sex Med* 2010; 7: 1668-1686 [PMID: 20388164 DOI: 10.1111/j.1743-6109.2010.01782.x]
- Andersson KE, Abdel-Hamid IA. Therapeutic targets for premature ejaculation. *Maturitas* 2011; 70: 26-33 [PMID: 21816550 DOI: 10.1016/j.maturitas.2011.06.007]
- Parnham A, Serefoglu EC. Retrograde ejaculation, painful ejaculation and hematospermia. *Transl Androl Urol* 2016; 5: 592-601 [PMID: 27652230 DOI: 10.21037/tau.2016.06.05]
- Phillips E, Carpenter C, Oates RD. Ejaculatory dysfunction. *Urol Clin North Am* 2014; 41: 115-128 [PMID: 24286771 DOI: 10.1016/j.ucl.2013.08.018]
- Clement P, Giuliano F. Physiology and Pharmacology of Ejaculation. *Basic Clin Pharmacol Toxicol* 2016; 119 Suppl 3: 18-25 [PMID: 26709195 DOI: 10.1111/bcpt.12546]

- 6 **Everaert K**, de Waard WI, Van Hoof T, Kiekens C, Mulliez T, D'herde C. Neuroanatomy and neurophysiology related to sexual dysfunction in male neurogenic patients with lesions to the spinal cord or peripheral nerves. *Spinal Cord* 2010; **48**: 182-191 [PMID: 20048757 DOI: 10.1038/sc.2009.172]
- 7 **Aumüller G**, Riva A. Morphology and functions of the human seminal vesicle. *Andrologia* 1992; **24**: 183-196 [PMID: 1642333 DOI: 10.1111/j.1439-0272.1992.tb02636.x]
- 8 **Witte LP**, Chapple CR, de la Rosette JJ, Michel MC. Cholinergic innervation and muscarinic receptors in the human prostate. *Eur Urol* 2008; **54**: 326-334 [PMID: 18160204 DOI: 10.1016/j.eururo.2007.12.007]
- 9 **Comarr AE**. Sexual function among patients with spinal cord injury. *Urol Int* 1970; **25**: 134-168 [PMID: 5422714 DOI: 10.1159/000279669]
- 10 **Gerstenberg TC**, Levin RJ, Wagner G. Erection and ejaculation in man. Assessment of the electromyographic activity of the bulbocavernosus and ischiocavernosus muscles. *Br J Urol* 1990; **65**: 395-402 [PMID: 2340374 DOI: 10.1111/j.1464-410x.1990.tb14764.x]
- 11 **Onuf B**. Notes on the arrangement and function of the cell groups in the sacral region of the spinal cord. *J Nerv Ment Dis* 1899; **26**: 498-504
- 12 **Truitt WA**, Coolen LM. Identification of a potential ejaculation generator in the spinal cord. *Science* 2002; **297**: 1566-1569 [PMID: 12202834 DOI: 10.1126/science.1073885]
- 13 **Staudt MD**, Truitt WA, McKenna KE, de Oliveira CV, Lehman MN, Coolen LM. A pivotal role of lumbar spinothalamic cells in the regulation of ejaculation via intraspinal connections. *J Sex Med* 2012; **9**: 2256-2265 [PMID: 22189051 DOI: 10.1111/j.1743-6109.2011.02574.x]
- 14 **Chéhense C**, Facchinetti P, Bahrami S, Andrey P, Soler JM, Chrétien F, Bernabé J, Clément P, Denys P, Giuliano F. Human spinal ejaculation generator. *Ann Neurol* 2017; **81**: 35-45 [PMID: 27917533 DOI: 10.1002/ana.24819]
- 15 **Corona G**, Jannini EA, Vignozzi L, Rastrelli G, Maggi M. The hormonal control of ejaculation. *Nat Rev Urol* 2012; **9**: 508-519 [PMID: 22869001 DOI: 10.1038/nrurol.2012.147]
- 16 **Stadler B**, Whittaker MR, Exintaris B, Middendorff R. Oxytocin in the Male Reproductive Tract; The Therapeutic Potential of Oxytocin-Agonists and-Antagonists. *Front Endocrinol (Lausanne)* 2020; **11**: 565731 [PMID: 33193084 DOI: 10.3389/fendo.2020.565731]
- 17 **Vignozzi L**, Filippi S, Morelli A, Luconi M, Jannini E, Forti G, Maggi M. Regulation of epididymal contractility during semen emission, the first part of the ejaculatory process: a role for estrogen. *J Sex Med* 2008; **5**: 2010-6; quiz 2017 [PMID: 18783525 DOI: 10.1111/j.1743-6109.2008.00914.x]
- 18 **Krüger TH**, Haake P, Chereath D, Knapp W, Janssen OE, Exton MS, Schedlowski M, Hartmann U. Specificity of the neuroendocrine response to orgasm during sexual arousal in men. *J Endocrinol* 2003; **177**: 57-64 [PMID: 12697037 DOI: 10.1677/joe.0.1770057]
- 19 **Krüger TH**, Hartmann U, Schedlowski M. Prolactinergic and dopaminergic mechanisms underlying sexual arousal and orgasm in humans. *World J Urol* 2005; **23**: 130-138 [PMID: 15889301 DOI: 10.1007/s00345-004-0496-7]
- 20 **Rastrelli G**, Corona G, Maggi M. Testosterone and sexual function in men. *Maturitas* 2018; **112**: 46-52 [PMID: 29704917 DOI: 10.1016/j.maturitas.2018.04.004]
- 21 **Keast JR**. Effects of testosterone on pelvic autonomic pathways: progress and pitfalls. *J Auton Nerv Syst* 2000; **79**: 67-73 [PMID: 10699636 DOI: 10.1016/s0165-1838(99)00087-9]
- 22 **Ye F**, McCoy SC, Ross HH, Bernardo JA, Beharry AW, Senf SM, Judge AR, Beck DT, Conover CF, Cannady DF, Smith BK, Yarrow JF, Borst SE. Transcriptional regulation of myotrophic actions by testosterone and trenbolone on androgen-responsive muscle. *Steroids* 2014; **87**: 59-66 [PMID: 24928725 DOI: 10.1016/j.steroids.2014.05.024]
- 23 **Gupta N**, Carvajal M, Jurewicz M, Gilbert BR. Bulbocavernosus muscle area as a novel marker for hypogonadism. *Asian J Urol* 2017; **4**: 3-9 [PMID: 29264199 DOI: 10.1016/j.ajur.2016.11.002]
- 24 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013; **36**: S67-74 [PMID: 23264425 DOI: 10.2337/dc13-S067]
- 25 **Ellenberg M**, Weber H. Retrograde ejaculation in diabetic neuropathy. *Ann Intern Med* 1966; **65**: 1237-1246 [PMID: 5928483 DOI: 10.7326/0003-4819-65-6-1237]
- 26 **Haddad WT Jr**, Moritsugu OT, Fornazari VR, Neto CAF, da Frota YB, Molina CAF, Elias J Jr, Pazin-Filho A, Muglia VF. Prevalence of vas deferens calcifications on abdominal CT examinations and association with systemic conditions. *AJR Am J Roentgenol* 2020; **215**: 1398-1402 [PMID: 33021834 DOI: 10.2214/AJR.19.22672]
- 27 **La Vignera S**, Condorelli RA, Vicari E, Lotti F, Favilla V, Morgia G, Maggi M, Calogero AE. Seminal vesicles and diabetic neuropathy: ultrasound evaluation after prolonged treatment with a selective phosphodiesterase-5 inhibitor. *Andrology* 2013; **1**: 245-250 [PMID: 23413137 DOI: 10.1111/j.2047-2927.2012.00025.x]
- 28 **La Vignera S**, Condorelli RA, Di Mauro M, Lo Presti D, Mongioli LM, Russo G, Calogero AE. Reproductive function in male patients with type 1 diabetes mellitus. *Andrology* 2015; **3**: 1082-1087 [PMID: 26446574 DOI: 10.1111/andr.12097]
- 29 **Hylmarova S**, Stechova K, Pavlinkova G, Peknicova J, Macek M, Kvapil M. The impact of type 1 diabetes mellitus on male sexual functions and sex hormone levels. *Endocr J* 2020; **67**: 59-71 [PMID: 31619592 DOI: 10.1507/endocrj.EJ19-0280]
- 30 **Gaunay G**, Nagler HM, Stember DS. Reproductive sequelae of diabetes in male patients. *Endocrinol Metab Clin North Am* 2013; **42**: 899-914 [PMID: 24286955 DOI: 10.1016/j.ecl.2013.07.003]

- 31 **Sachs BD**, Baum MJ, Melman A. Normal sexual behavior and penile reflexes in long-term diabetic male rats. *Arch Androl* 1982; **9**: 351-353 [PMID: 7165414 DOI: 10.3109/01485018208990261]
- 32 **Clark JT**. Sexual function in altered physiological states: comparison of effects of hypertension, diabetes, hyperprolactinemia, and others to "normal" aging in male rats. *Neurosci Biobehav Rev* 1995; **19**: 279-302 [PMID: 7630583 DOI: 10.1016/0149-7634(94)00058-9]
- 33 **Scarano WR**, Messias AG, Oliva SU, Klinefelter GR, Kempinas WG. Sexual behaviour, sperm quantity and quality after short-term streptozotocin-induced hyperglycaemia in rats. *Int J Androl* 2006; **29**: 482-488 [PMID: 16524366 DOI: 10.1111/j.1365-2605.2006.00682.x]
- 34 **Steger RW**, Kienast SG. Effect of continuous versus delayed insulin replacement on sex behavior and neuroendocrine function in diabetic male rats. *Diabetes* 1990; **39**: 942-948 [PMID: 1973672 DOI: 10.2337/diab.39.8.942]
- 35 **Murray FT**, Johnson RD, Sciadini M, Katovich MJ, Rountree J, Jewett H. Erectile and copulatory dysfunction in chronically diabetic BB/WOR rats. *Am J Physiol* 1992; **263**: E151-E157 [PMID: 1636693 DOI: 10.1152/ajpendo.1992.263.1.E151]
- 36 **McVary KT**, Rathnau CH, McKenna KE. Sexual dysfunction in the diabetic BB/WOR rat: a role of central neuropathy. *Am J Physiol* 1997; **272**: R259-R267 [PMID: 9039017 DOI: 10.1152/ajpregu.1997.272.1.R259]
- 37 **Ebiko M**, Yonezawa A, Yoshizumi M. Changes in ejaculatory capacity in the type I diabetic rats. *Jpn J Sex Med* 2006; **21**: 221-232
- 38 **Yonezawa A**, Ebiko M, Yoshizumi M, Ise SN, Watanabe C, Mizoguchi H, Iwasaki M, Kimura Y, Sakurada S. Effects of insulin replacement on ejaculatory dysfunction in streptozotocin-induced diabetic rats. *Int J Urol* 2009; **16**: 208-211 [PMID: 19183231 DOI: 10.1111/j.1442-2042.2008.02214.x]
- 39 **Suresh S**, Prakash S. Effect of *Mucuna pruriens* (Linn.) on sexual behavior and sperm parameters in streptozotocin-induced diabetic male rat. *J Sex Med* 2012; **9**: 3066-3078 [PMID: 20456630 DOI: 10.1111/j.1743-6109.2010.01831.x]
- 40 **De A**, Singh MF, Singh V, Ram V, Bisht S. Treatment effect of l-Norvaline on the sexual performance of male rats with streptozotocin induced diabetes. *Eur J Pharmacol* 2016; **771**: 247-254 [PMID: 26671005 DOI: 10.1016/j.ejphar.2015.12.008]
- 41 **Shi GJ**, Zheng J, Wu J, Qiao HQ, Chang Q, Niu Y, Sun T, Li YX, Yu JQ. Protective effects of *Lycium barbarum* polysaccharide on male sexual dysfunction and fertility impairments by activating hypothalamic pituitary gonadal axis in streptozotocin-induced type-1 diabetic male mice. *Endocr J* 2017; **64**: 907-922 [PMID: 28794341 DOI: 10.1507/endocrj.EJ16-0430]
- 42 **Li ZM**, Liu N, Jiang YP, Yang JM, Zheng J, Sun M, Li YX, Sun T, Wu J, Yu JQ. Vitexin alleviates streptozotocin-induced sexual dysfunction and fertility impairments in male mice *via* modulating the hypothalamus-pituitary-gonadal axis. *Chem Biol Interact* 2019; **297**: 119-129 [PMID: 30365938 DOI: 10.1016/j.cbi.2018.10.013]
- 43 **Lert-Amornpat T**, Maketon C, Fungfuang W. Effect of *Kaempferia parviflora* on sexual performance in streptozotocin-induced diabetic male rats. *Andrologia* 2017; **49** [PMID: 28295466 DOI: 10.1111/and.12770]
- 44 **Fernández-Collazo EL**, Foglia VG. Sexual behavior of the male diabetic rat. *Physiol Behav* 1970; **5**: 1451-1454 [PMID: 5524534 DOI: 10.1016/0031-9384(70)90135-6]
- 45 **Hassan AA**, Hassouna MM, Taketo T, Gagnon C, Elhilali MM. The effect of diabetes on sexual behavior and reproductive tract function in male rats. *J Urol* 1993; **149**: 148-154 [PMID: 8417201 DOI: 10.1016/s0022-5347(17)36028-7]
- 46 **Pontes DA**, Fernandes GS, Piffer RC, Gerardin DC, Pereira OC, Kempinas WG. Ejaculatory dysfunction in streptozotocin-induced diabetic rats: the role of testosterone. *Pharmacol Rep* 2011; **63**: 130-138 [PMID: 21441620 DOI: 10.1016/s1734-1140(11)70407-8]
- 47 **Ghaheri M**, Miraghaee S, Babaei A, Mohammadi B, Kahrizi D, Saivosh Haghghi ZM, Bahrami G. Effect of *Stevia rebaudiana* Bertoni extract on sexual dysfunction in Streptozotocin-induced diabetic male rats. *Cell Mol Biol (Noisy-le-grand)* 2018; **64**: 6-10 [PMID: 29433621 DOI: 10.14715/cmb/2018.64.2.2]
- 48 **Minaz N**, Razdan R, Hammock BD, Mujwar S, Goswami SK. Impact of diabetes on male sexual function in streptozotocin-induced diabetic rats: Protective role of soluble epoxide hydrolase inhibitor. *Biomed Pharmacother* 2019; **115**: 108897 [PMID: 31102913 DOI: 10.1016/j.biopha.2019.108897]
- 49 **Yagihashi S**, Sima AA. Diabetic autonomic neuropathy in the BB rat. Ultrastructural and morphometric changes in sympathetic nerves. *Diabetes* 1985; **34**: 558-564 [PMID: 4007283 DOI: 10.2337/diab.34.6.558]
- 50 **Tomlinson DR**, Gillon KR, Smith MG. Axonal transport of noradrenaline and noradrenergic transmission in rats with streptozotocin-induced diabetes. *Diabetologia* 1982; **22**: 199-204 [PMID: 6176490 DOI: 10.1007/BF00283753]
- 51 **Longhurst PA**, Brotcke TP, Burrell CL, Belis JA. Comparison of the effects of castration and streptozotocin-induced diabetes mellitus on contractile responses of the rat vas deferens. *Pharmacology* 1989; **38**: 253-262 [PMID: 2755965 DOI: 10.1159/000138544]
- 52 **Kaschube M**, Möller-Hartmann H, Zetler G. The field-stimulated vas deferens of the streptozotocin-diabetic mouse: effects of prazosin, alpha, beta-methylene ATP, and variation of stimulation parameters. *J Neural Transm* 1989; **77**: 171-180 [PMID: 2760603 DOI: 10.1007/BF01248930]
- 53 **Kamata K**, Kirisawa H. Changes in electrophysiological properties and noradrenaline response in

- vas deferens of diabetic rats. *Eur J Pharmacol* 1998; **350**: 237-241 [PMID: 9696413 DOI: 10.1016/s0014-2999(98)00271-4]
- 54 **Güneş A**, Ceylan A, Sarioglu Y, Stefek M, Bauer V, Karasu C; Antioxidants in Diabetes-induced Complications (ADIC) Study Group. Reactive oxygen species mediate abnormal contractile response to sympathetic nerve stimulation and noradrenaline in the vas deferens of chronically diabetic rats: effects of in vivo treatment with antioxidants. *Fundam Clin Pharmacol* 2005; **19**: 73-79 [PMID: 15660962 DOI: 10.1111/j.1472-8206.2004.00312.x]
- 55 **Tsounapi P**, Honda M, Dimitriadis F, Shimizu S, Shiomi T, Hikita K, Saito M, Tomita S, Sofikitis N, Takenaka A. Antioxidant treatment ameliorates diabetes-induced dysfunction of the vas deferens in a rat model. *Andrologia* 2018; **50** [PMID: 28224697 DOI: 10.1111/and.12795]
- 56 **Sakai Y**, Honda H. Hyperactivity of Ca channels in vasa deferentia smooth muscle of diabetic rats. *Pharmacol Biochem Behav* 1987; **27**: 227-229 [PMID: 2442778 DOI: 10.1016/0091-3057(87)90562-4]
- 57 **Sakai Y**, Aihara K, Honda H, Inazu M. Calcium mobilization and phosphatidylinositol turnover in vas deferens smooth muscle of diabetic rats. *Eur J Pharmacol* 1989; **162**: 475-481 [PMID: 2744081 DOI: 10.1016/0014-2999(89)90338-5]
- 58 **Elbadawi A**. Ultrastructure of vesicourethral innervation. II. Postganglionic axoaxonal synapses in intrinsic innervation of the vesicourethral lissosphincter: a new structural and functional concept in micturition. *J Urol* 1984; **131**: 781-790 [PMID: 6708203 DOI: 10.1016/s0022-5347(17)50624-2]
- 59 **Fowler CJ**, Griffiths D, de Groat WC. The neural control of micturition. *Nat Rev Neurosci* 2008; **9**: 453-466 [PMID: 18490916 DOI: 10.1038/nrn2401]
- 60 **Torimoto K**, Hirao Y, Matsuyoshi H, de Groat WC, Chancellor MB, Yoshimura N. alpha1-Adrenergic mechanism in diabetic urethral dysfunction in rats. *J Urol* 2005; **173**: 1027-1032 [PMID: 15711370 DOI: 10.1097/01.ju.0000146268.45662.36]
- 61 **Sandrini M**, Vitale G, Vergoni AV, Ottani A, Bertolini A. Streptozotocin-induced diabetes provokes changes in serotonin concentration and on 5-HT1A and 5-HT2 receptors in the rat brain. *Life Sci* 1997; **60**: 1393-1397 [PMID: 9096260 DOI: 10.1016/s0024-3205(97)00084-2]
- 62 **Abraham PM**, Anju TR, Jayanarayanan S, Paulose CS. Serotonergic receptor upregulation in cerebral cortex and down regulation in brainstem of streptozotocin induced diabetic rats: antagonism by pyridoxine and insulin. *Neurosci Lett* 2010; **483**: 23-27 [PMID: 20655360 DOI: 10.1016/j.neulet.2010.07.042]
- 63 **Martin-Tuite P**, Shindel AW. Management options for premature ejaculation and delayed ejaculation in men. *Sex Med Rev* 2020; **8**: 473-485 [PMID: 31668585 DOI: 10.1016/j.sxmr.2019.09.002]
- 64 **Kühn-Velten N**, Waldenburger D, Staib W. Evaluation of steroid biosynthetic lesions in isolated Leydig cells from the testes of streptozotocin-diabetic rats. *Diabetologia* 1982; **23**: 529-533 [PMID: 6295863 DOI: 10.1007/BF00254305]
- 65 **Anderson JE**, Thliveris JA. Morphometry and cytochemistry of Leydig cells in experimental diabetes. *Am J Anat* 1987; **180**: 41-48 [PMID: 3310596 DOI: 10.1002/aja.1001800104]
- 66 **Ricci G**, Catizone A, Esposito R, Pisanti FA, Vietri MT, Galdieri M. Diabetic rat testes: morphological and functional alterations. *Andrologia* 2009; **41**: 361-368 [PMID: 19891634 DOI: 10.1111/j.1439-0272.2009.00937.x]
- 67 **Murray FT**, Cameron DF, Orth JM, Katovich MJ. Gonadal dysfunction in the spontaneously diabetic BB rat: alterations of testes morphology, serum testosterone and LH. *Horm Metab Res* 1985; **17**: 495-501 [PMID: 4065811 DOI: 10.1055/s-2007-1013588]
- 68 **Cameron DF**, Rountree J, Schultz RE, Repetta D, Murray FT. Sustained hyperglycemia results in testicular dysfunction and reduced fertility potential in BBWor diabetic rats. *Am J Physiol* 1990; **259**: E881-E889 [PMID: 2260654 DOI: 10.1152/ajpendo.1990.259.6.E881]
- 69 **Ohta T**, Katsuda Y, Miyajima K, Sasase T, Kimura S, Tong B, Yamada T. Gender differences in metabolic disorders and related diseases in spontaneously diabetic Torii-Lepr(fa) rats. *J Diabetes Res* 2014; **2014**: 841957 [PMID: 24892034 DOI: 10.1155/2014/841957]
- 70 **Nakane Y**, Kemmochi Y, Ogawa N, Sasase T, Ohta T, Higami Y, Fukai F. Hyperglycemia contributes to the development of Leydig cell hyperplasia in male Spontaneously Diabetic Torii rats. *J Toxicol Pathol* 2020; **33**: 121-129 [PMID: 32425345 DOI: 10.1293/tox.2019-0088]
- 71 **Seethalakshmi L**, Menon M, Diamond D. The effect of streptozotocin-induced diabetes on the neuroendocrine-male reproductive tract axis of the adult rat. *J Urol* 1987; **138**: 190-194 [PMID: 3599211 DOI: 10.1016/s0022-5347(17)43042-4]
- 72 **Wolfe A**, Divall S, Wu S. The regulation of reproductive neuroendocrine function by insulin and insulin-like growth factor-1 (IGF-1). *Front Neuroendocrinol* 2014; **35**: 558-572 [PMID: 24929098 DOI: 10.1016/j.yfme.2014.05.007]
- 73 **Oksanen A**. Testicular lesions of streptozotocin diabetic rats. *Horm Res* 1975; **6**: 138-144 [PMID: 130334 DOI: 10.1159/000178671]
- 74 **Sudha S**, Valli G, Julie PM, Arunakaran J, Govindarajulu P, Balasubramanian K. Influence of streptozotocin-induced diabetes and insulin treatment on the pituitary-testicular axis during sexual maturation in rats. *Exp Clin Endocrinol Diabetes* 2000; **108**: 14-20 [PMID: 10768827 DOI: 10.1055/s-0032-1329210]
- 75 **Ballester J**, Muñoz MC, Domínguez J, Rigau T, Guinovart JJ, Rodríguez-Gil JE. Insulin-dependent diabetes affects testicular function by FSH- and LH-linked mechanisms. *J Androl* 2004; **25**: 706-719 [PMID: 15292100 DOI: 10.1002/j.1939-4640.2004.tb02845.x]

- 76 **Neirijnck Y**, Calvel P, Kilcoyne KR, Kühne F, Stévant I, Griffeth RJ, Pitetti JL, Andric SA, Hu MC, Pralong F, Smith LB, Nef S. Insulin and IGF1 receptors are essential for the development and steroidogenic function of adult Leydig cells. *FASEB J* 2018; **32**: 3321-3335 [PMID: 29401624 DOI: 10.1096/fj.201700769RR]
- 77 **Steger RW**. Testosterone replacement fails to reverse the adverse effects of streptozotocin-induced diabetes on sexual behavior in the male rat. *Pharmacol Biochem Behav* 1990; **35**: 577-582 [PMID: 2140195 DOI: 10.1016/0091-3057(90)90293-q]
- 78 **Nutsch VL**, Will RG, Tobiansky DJ, Reilly MP, Gore AC, Dominguez JM. Age-related changes in sexual function and steroid-hormone receptors in the medial preoptic area of male rats. *Horm Behav* 2017; **96**: 4-12 [PMID: 28882473 DOI: 10.1016/j.yhbeh.2017.08.008]
- 79 **Murashima A**, Kishigami S, Thomson A, Yamada G. Androgens and mammalian male reproductive tract development. *Biochim Biophys Acta* 2015; **1849**: 163-170 [PMID: 24875095 DOI: 10.1016/j.bbagr.2014.05.020]
- 80 **Dabaja AA**, Wosnitzer MS, Mielnik A, Bolyakov A, Schlegel PN, Paduch DA. Bulbocavernosus muscle area measurement: a novel method to assess androgenic activity. *Asian J Androl* 2014; **16**: 618-622 [PMID: 24589463 DOI: 10.4103/1008-682X.123681]
- 81 **Corona G**, Jannini EA, Mannucci E, Fisher AD, Lotti F, Petrone L, Balercia G, Bandini E, Chiarini V, Forti G, Maggi M. Different testosterone levels are associated with ejaculatory dysfunction. *J Sex Med* 2008; **5**: 1991-1998 [PMID: 18399946 DOI: 10.1111/j.1743-6109.2008.00803.x]
- 82 **Paduch DA**, Polzer PK, Ni X, Basaria S. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: A randomized controlled trial. *J Clin Endocrinol Metab* 2015; **100**: 2956-2962 [PMID: 26158605 DOI: 10.1210/jc.2014-4434]
- 83 **Damassa DA**, Smith ER, Tennent B, Davidson JM. The relationship between circulating testosterone levels and male sexual behavior in rats. *Horm Behav* 1977; **8**: 275-286 [PMID: 881168 DOI: 10.1016/0018-506x(77)90002-2]
- 84 **Saenz de Tejada I**, Goldstein I. Diabetic penile neuropathy. *Urol Clin North Am* 1988; **15**: 17-22 [PMID: 2830692]
- 85 **Steger RW**, Amador A, Lam E, Rathert J, Weis J, Smith MS. Streptozotocin-induced deficits in sex behavior and neuroendocrine function in male rats. *Endocrinology* 1989; **124**: 1737-1743 [PMID: 2522388 DOI: 10.1210/endo-124-4-1737]
- 86 **Al-Roujaye A**. Improvement of sexual behavior, sperm quantity and quality by Quercetin in streptozotocin-induced diabetic erectile dysfunction. *Asian Pac J Reprod* 2017; **6**: 6-12 [DOI: 10.12980/apjr.6.20170102]
- 87 **Kashif S**, Razdan R, Jamwal R, Goswami SK. Allantoin alleviates male sexual dysfunction in diabetic rats through augmenting the level of testosterone. *J Young Pharm* 2018; **10**: 57-61 [DOI: 10.5530/jyp.2018.10.14]
- 88 **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**: 352-357 [PMID: 31477853 DOI: 10.1038/s41443-019-0188-x]
- 89 **Khan HL**, Bhatti S, Abbas S, Khan YL, Gonzalez RMM, Aslamkhan M, Gonzalez GR, Aydin HH. 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 [PMID: 29556396 DOI: 10.1186/s12610-018-0068-0]
- 90 **Malavige LS**, Wijesekara P, Seneviratne Epa D, Ranasinghe P, Levy JC. Ethnic differences in sexual dysfunction among diabetic and nondiabetic males: the Oxford Sexual Dysfunction Study. *J Sex Med* 2013; **10**: 500-508 [PMID: 22925588 DOI: 10.1111/j.1743-6109.2012.02911.x]
- 91 **El-Sakka AI**. Premature ejaculation in non-insulindependent diabetic patients. *Int J Androl* 2003; **26**: 329-334 [DOI: 10.1111/j.1365-2605.2003.00433.x]
- 92 **Majzoub A**, Arafa M, Al-Said S, Dabbous Z, Aboulsoud S, Khalafalla K, Elbardisi H. Premature ejaculation in type II diabetes mellitus patients: association with glycemic control. *Transl Androl Urol* 2016; **5**: 248-254 [PMID: 27141454 DOI: 10.21037/tau.2016.03.11]
- 93 **Malavige LS**, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Fernando DJ, Levy JC. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. *J Sex Med* 2008; **5**: 2125-2134 [PMID: 18624974 DOI: 10.1111/j.1743-6109.2008.00907.x]
- 94 **Olamoyegun MA**, Ayodele AO, Yemi FE, Akinyele AT. Prevalence of premature ejaculation among patients with type 2 diabetes in a tertiary health institution. *J Diabetes Mellitus* 2020; **10**: 88-97 [DOI: 10.4236/jdm.2020.102008]
- 95 **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 [PMID: 21612653 DOI: 10.1186/1477-7827-9-70]
- 96 **Bellastella G**, Maiorino MI, Olita L, Della Volpe E, Giugliano D, Esposito K. Premature ejaculation is associated with glycemic control in Type 1 diabetes. *J Sex Med* 2015; **12**: 93-99 [PMID: 25424355 DOI: 10.1111/jsm.12755]
- 97 **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**: 2065-2073 [PMID: 25041930 DOI: 10.1111/jsm.12601]
- 98 **Dinulovic D**, Radonjic G. Diabetes mellitus/male infertility. *Arch Androl* 1990; **25**: 277-293 [PMID: 2285351 DOI: 10.3109/01485019008987617]
- 99 **Dunsmuir WD**, Holmes SA. The aetiology and management of erectile, ejaculatory, and fertility

- problems in men with diabetes mellitus. *Diabet Med* 1996; **13**: 700-708 [PMID: 8862943 DOI: 10.1002/(SICI)1096-9136(199608)13:8<700::AID-DIA174>3.0.CO;2-8]
- 100 **Condorelli RA**, Vicari E, Calogero AE, La Vignera S. Male accessory gland inflammation prevalence in type 2 diabetic patients with symptoms possibly reflecting autonomic neuropathy. *Asian J Androl* 2014; **16**: 761-766 [PMID: 24799635 DOI: 10.4103/1008-682X.125911]
- 101 **La Vignera S**, Condorelli RA, Cannarella R, Giacone F, Mongioi' LM, Cimino L, Defeudis G, Mazzilli R, Calogero AE. Urogenital infections in patients with diabetes mellitus: Beyond the conventional aspects. *Int J Immunopathol Pharmacol* 2019; **33**: 2058738419866582 [PMID: 32031031 DOI: 10.1177/2058738419866582]
- 102 **Pop-Busui R**, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; **40**: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]
- 103 **Culver GJ**, Tannenhaus J. Calcification of the vas deferens in diabetes. *J Am Med Assoc* 1960; **173**: 648-651 [PMID: 13813264 DOI: 10.1001/jama.1960.03020240036006]
- 104 **Tsuno MM**, Gerber JM, Pokras RS. Calcification of vas deferens associated with diabetes mellitus. *J Manipulative Physiol Ther* 1991; **14**: 70-73 [PMID: 2002291]
- 105 **Gianatti EJ**, Dupuis P, Hoermann R, Zajac JD, Grossmann M. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab* 2014; **99**: 3821-3828 [PMID: 24978674 DOI: 10.1210/jc.2014-1872]
- 106 **Morgentaler A**, Polzer P, Althof S, Bolyakov A, Donatucci C, Ni X, Patel AB, Basaria S. Delayed Ejaculation and Associated Complaints: Relationship to Ejaculation Times and Serum Testosterone Levels. *J Sex Med* 2017; **14**: 1116-1124 [PMID: 28807505 DOI: 10.1016/j.jsxm.2017.06.013]
- 107 **Burke JP**, Jacobson DJ, McGree ME, Nehra A, Roberts RO, Girman CJ, Lieber MM, Jacobsen SJ. Diabetes and sexual dysfunction: results from the Olmsted County study of urinary symptoms and health status among men. *J Urol* 2007; **177**: 1438-1442 [PMID: 17382749 DOI: 10.1016/j.juro.2006.11.059]
- 108 **Corona G**, Mannucci E, Petrone L, Ricca V, Balercia G, Mansani R, Chiarini V, Giommi R, Forti G, Maggi M. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. *Int J Impot Res* 2006; **18**: 190-197 [PMID: 16136189 DOI: 10.1038/sj.ijir.3901391]
- 109 **Corona G**, Mannucci E, Petrone L, Fisher AD, Balercia G, De Scisciolo G, Pizzocaro A, Giommi R, Chiarini V, Forti G, Maggi M. Psychobiological correlates of delayed ejaculation in male patients with sexual dysfunctions. *J Androl* 2006; **27**: 453-458 [PMID: 16339452 DOI: 10.2164/jandrol.05154]
- 110 **Klebanow D**, Macleod J. Semen quality and certain disturbances of reproduction in diabetic men. *Fertil Steril* 1960; **11**: 255-261 [PMID: 14409622 DOI: 10.1016/s0015-0282(16)33781-5]
- 111 **Greene LF**, Kelalis PP. Retrograde ejaculation of semen dueto diabetic neuropathy. *J Urol* 1967; **98**: 696 [PMID: 6080049]
- 112 **Koyanagi T**. Studies on the sphincteric system located distally in the urethra: the external urethral sphincter revisited. *J Urol* 1980; **124**: 400-406 [PMID: 6107390 DOI: 10.1016/s0022-5347(17)55468-3]
- 113 **Cao N**, Gu B, Gotoh D, Yoshimura N. Time-Dependent Changes of Urethral Function in Diabetes Mellitus: A Review. *Int Neurol J* 2019; **23**: 91-99 [PMID: 31260608 DOI: 10.5213/inj.1938050.025]
- 114 **Basile Fasolo C**, Mirone V, Gentile V, Parazzini F, Ricci E; Andrology Prevention Week centers; Italian Society of Andrology (SIA). Premature ejaculation: prevalence and associated conditions in a sample of 12,558 men attending the andrology prevention week 2001--a study of the Italian Society of Andrology (SIA). *J Sex Med* 2005; **2**: 376-382 [PMID: 16422869 DOI: 10.1111/j.1743-6109.2005.20350.x]
- 115 **Corona G**, Rastrelli G, Limoncin E, Sforza A, Jannini EA, Maggi M. Interplay Between Premature Ejaculation and Erectile Dysfunction: A Systematic Review and Meta-Analysis. *J Sex Med* 2015; **12**: 2291-2300 [PMID: 26552599 DOI: 10.1111/jsm.13041]
- 116 **Lee SW**, Lee JH, Sung HH, Park HJ, Park JK, Choi SK, Kam SC. The prevalence of premature ejaculation and its clinical characteristics in Korean men according to different definitions. *Int J Impot Res* 2013; **25**: 12-17 [PMID: 22931761 DOI: 10.1038/ijir.2012.27]
- 117 **Hoffman RP**. Sympathetic mechanisms of hypoglycemic counterregulation. *Curr Diabetes Rev* 2007; **3**: 185-193 [PMID: 18220670 DOI: 10.2174/157339907781368995]
- 118 **Xia J**, Zhang Q, Wang Y, Luan J, Yang J, Cong R, Wang Z, Song N. Association of NE, leptin, and 5-HT with electrophysiological parameters in patients with primary premature ejaculation. *Andrology* 2020; **8**: 1070-1075 [PMID: 32068350 DOI: 10.1111/andr.12773]
- 119 **Serefoglu EC**, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, Becher EF, Dean J, Giuliano F, Hellstrom WJ, Giraldi A, Glina S, Incrocci L, Jannini E, McCabe M, Parish S, Rowland D, Segraves RT, Sharlip I, Torres LO. 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. *Sex Med* 2014; **2**: 41-59 [PMID: 25356301 DOI: 10.1002/sm2.27]
- 120 **Hatzimouratidis K**, Giuliano F, Moncada I, Muneer A, Salonia A, Verze P, Guideline Associates: Parnham A, Serefoglu EC. EAU guidelines on erectile dysfunction, premature ejaculation, penile

- curvature and priapism. Arnhem, The Netherlands: EAU Guidelines Office; 2018. Available from: <https://www.uroweb.org/guideline/male-sexual-dysfunction>
- 121 **McMahon CG**, Giuliano F, Dean J, Hellstrom WJ, Bull S, Tesfaye F, Sharma O, Rivas DA, Aquilina JW. Efficacy and safety of dapoxetine in men with premature ejaculation and concomitant erectile dysfunction treated with a phosphodiesterase type 5 inhibitor: randomized, placebo-controlled, phase III study. *J Sex Med* 2013; **10**: 2312-2325 [PMID: 23845016 DOI: 10.1111/jsm.12236]
 - 122 **Jiann BP**, Huang YJ. Assessing satisfaction in men with premature ejaculation after dapoxetine treatment in real-world practice. *Int J Clin Pract* 2015; **69**: 1326-1333 [PMID: 26194604 DOI: 10.1111/ijcp.12700]
 - 123 **Tuken M**, Culha MG, Serefoglu EC. Efficacy and safety of dapoxetine/sildenafil combination tablets in the treatment of men with premature ejaculation and concomitant erectile dysfunction-DAP-SPEED Study. *Int J Impot Res* 2019; **31**: 92-96 [PMID: 30705437 DOI: 10.1038/s41443-019-0122-2]
 - 124 **Abdel-Hamid IA**, Ali OI. Delayed Ejaculation: Pathophysiology, Diagnosis, and Treatment. *World J Mens Health* 2018; **36**: 22-40 [PMID: 29299903 DOI: 10.5534/wjmh.17051]
 - 125 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013
 - 126 **Kaplan HS**. The new sex therapy. London, UK, Baillière Tindall; 1974
 - 127 **Laumann EO**, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; **281**: 537-544 [PMID: 10022110 DOI: 10.1001/jama.281.6.537]
 - 128 **Di Sante S**, Mollaioli D, Gravina GL, Ciocca G, Limoncin E, Carosa E, Lenzi A, Jannini EA. Epidemiology of delayed ejaculation. *Transl Androl Urol* 2016; **5**: 541-548 [PMID: 27652226 DOI: 10.21037/tau.2016.05.10]
 - 129 **Jangir RN**, Jain GC. Diabetes mellitus induced impairment of male reproductive functions: a review. *Curr Diabetes Rev* 2014; **10**: 147-157 [PMID: 24919656 DOI: 10.2174/1573399810666140606111745]
 - 130 **Salma N**. Sexual dysfunctions as self-reported by diabetic- type-2 men: An Andrology clinic-based study in Alexandria, Egypt. *Am J Med Biol Res* 2013; **1**: 50-57 [DOI: 10.12691/ajmbr-1-3-1]
 - 131 **Gerig NE**, Meacham RB, Ohl DA. Use of electroejaculation in the treatment of ejaculatory failure secondary to diabetes mellitus. *Urology* 1997; **49**: 239-242 [PMID: 9037287 DOI: 10.1016/S0090-4295(96)00444-X]
 - 132 **Fairburn CG**, Wu FC, McCulloch DK, Borseley DQ, Ewing DJ, Clarke BF, Bancroft JH. The clinical features of diabetic impotence: a preliminary study. *Br J Psychiatry* 1982; **140**: 447-452 [PMID: 7104528 DOI: 10.1192/bjp.140.5.447]
 - 133 **Butcher MJ**, Welliver RC Jr, Sadowski D, Botchway A, Köhler TS. How is delayed ejaculation defined and treated in North America? *Andrology* 2015; **3**: 626-631 [PMID: 26013106 DOI: 10.1111/andr.12041]
 - 134 **Abdel-Hamid IA**, Elsaied MA, Mostafa T. The drug treatment of delayed ejaculation. *Transl Androl Urol* 2016; **5**: 576-591 [PMID: 27652229 DOI: 10.21037/tau.2016.05.05]
 - 135 **Agochukwu-Mmonu N**, Pop-Busui R, Wessells H, Sarma AV. Autonomic neuropathy and urologic complications in diabetes. *Auton Neurosci* 2020; **229**: 102736 [PMID: 33197694 DOI: 10.1016/j.autneu.2020.102736]
 - 136 **Lu S**, Cui Y, Li X, Zhang H, Hu J, Liu J, Chen ZJ. Sperm retrieval in anejaculatory diabetic men who failed in drug treatment and penile vibratory stimulation during blood sugar under control. *Andrologia* 2014; **46**: 370-373 [PMID: 23488950 DOI: 10.1111/and.12087]
 - 137 **Castle SM**, Jenkins LC, Ibrahim E, Aballa TC, Lynne CM, Brackett NL. Safety and efficacy of a new device for inducing ejaculation in men with spinal cord injuries. *Spinal Cord* 2014; **52** Suppl 2: S27-S29 [PMID: 25082380 DOI: 10.1038/sc.2014.110]
 - 138 **Lucas MG**, Hargreave TB, Edmond P, Creasey GH, McParland M, Seager SW. Sperm retrieval by electro-ejaculation. Preliminary experience in patients with secondary anejaculation. *Br J Urol* 1991; **67**: 191-194 [PMID: 2004235 DOI: 10.1111/j.1464-410x.1991.tb15108.x]
 - 139 **Hovatta O**, Reima I, Foudila T, Butzow T, Johansson K, von Smitten K. Vas deferens aspiration and intracytoplasmic injection of frozen-thawed spermatozoa in a case of anejaculation in a diabetic man. *Hum Reprod* 1996; **11**: 334-335 [PMID: 8671220 DOI: 10.1093/humrep/11.2.334]
 - 140 **Fang J**, Shu L, Cai L, Cui Y, Liu J, Yang X. Intracytoplasmic sperm injection outcomes in patients with orgasmic dysfunction and anejaculation by percutaneous epididymal sperm aspiration (PESA). *Ann Transl Med* 2020; **8**: 1214 [PMID: 33178746 DOI: 10.21037/atm-20-1121a]
 - 141 **Alrabeeh K**, Yafi F, Flageole C, Phillips S, Wachter A, Bissonnette F, Kadoch IJ, Zini A. Testicular sperm aspiration for nonazoospermic men: sperm retrieval and intracytoplasmic sperm injection outcomes. *Urology* 2014; **84**: 1342-1346 [PMID: 25432825 DOI: 10.1016/j.urology.2014.08.032]
 - 142 **Jefferys A**, Siassakos D, Wardle P. The management of retrograde ejaculation: a systematic review and update. *Fertil Steril* 2012; **97**: 306-312 [PMID: 22177462 DOI: 10.1016/j.fertnstert.2011.11.019]
 - 143 **Kam J**, Tsang VH, Chalasani V. Retrograde Ejaculation: A Rare Presenting Symptom of Type 1 Diabetes Mellitus. *Urol Case Rep* 2017; **10**: 9-10 [PMID: 27818945 DOI: 10.1016/j.eucr.2016.10.008]
 - 144 **Takahashi Y**, Okawa S. Investigation of sexual life in type I diabetic patients. *Jpn J Impot Res*

2000; **15**: 263-264

- 145 **Kurbatov D**, Russo GI, Galstyan GR, Rozhivanov R, Lepetukhin A, Dubsky S, Shwartz YG, Cimino S, Morgia G, Sansalone S. Correction of Retrograde Ejaculation in Patients with Diabetes Mellitus Using Endourethral Collagen Injection: Preliminary Results. *J Sex Med* 2015; **12**: 2126-2129 [PMID: [26553413](#) DOI: [10.1111/jsm.13024](#)]
- 146 **Otani T**. Clinical review of ejaculatory dysfunction. *Reprod Med Biol* 2019; **18**: 331-343 [PMID: [31607793](#) DOI: [10.1002/rmb2.12289](#)]
- 147 **Ibragimov AZ**, Aliev TA, Abdullaev KI, Mirza-Zade VA. Sostoianie zamykatel'nogo apparata mochevogo puzyria pri retrogradnoi éiakuliatsii u bol'nykh sakharnym diabetom [The function of the closure apparatus of the bladder in retrograde ejaculation in diabetics]. *Urol Nefrol (Mosk)* 1990; **65**: 68 [PMID: [2396344](#)]
- 148 **Mazzilli R**, Defeudis G, Olana S, Zamponi V, Macera M, Mazzilli F. The role of ejaculatory dysfunction on male infertility. *Clin Ter* 2020; **171**: e523-e527 [PMID: [33151251](#) DOI: [10.7417/CT.2020.2267](#)]
- 149 **McMahon CG**. Disorders of Male Orgasm and Ejaculation. In: Wein AJ, Kavoussi LR, Partin AW. Campbell-Walsh Urology. Philadelphia: Elsevier, 2016: 692-708
- 150 **Fedder J**, Kaspersen MD, Brandslund I, Højgaard A. Retrograde ejaculation and sexual dysfunction in men with diabetes mellitus: a prospective, controlled study. *Andrology* 2013; **1**: 602-606 [PMID: [23606485](#) DOI: [10.1111/j.2047-2927.2013.00083.x](#)]
- 151 **McMahon CG**, Abdo C, Incrocci L, Perelman M, Rowland D, Waldinger M, Xin ZC. Disorders of orgasm and ejaculation in men. *J Sex Med* 2004; **1**: 58-65 [PMID: [16422984](#) DOI: [10.1111/j.1743-6109.2004.10109.x](#)]
- 152 **Andaloro VA Jr**, Dube A. Treatment of retrograde ejaculation with brompheniramine. *Urology* 1975; **5**: 520-522 [PMID: [1129870](#) DOI: [10.1016/0090-4295\(75\)90080-1](#)]
- 153 **Budd HA Jr**. Letter: Brompheniramine in treatment of retrograde ejaculation. *Urology* 1975; **6**: 131 [PMID: [1145917](#) DOI: [10.1016/0090-4295\(75\)90614-7](#)]
- 154 **Stewart BH**, Bergant JA. Correction of retrograde ejaculation by sympathomimetic medication: preliminary report. *Fertil Steril* 1974; **25**: 1073-1074 [PMID: [4430388](#) DOI: [10.1016/s0015-0282\(16\)40816-2](#)]
- 155 **Gilja I**, Parazajder J, Radej M, Cvitković P, Kovacic M. Retrograde ejaculation and loss of emission: possibilities of conservative treatment. *Eur Urol* 1994; **25**: 226-228 [PMID: [8200405](#) DOI: [10.1159/000475288](#)]
- 156 **Arafa M**, El Tabie O. Medical treatment of retrograde ejaculation in diabetic patients: a hope for spontaneous pregnancy. *J Sex Med* 2008; **5**: 194-198 [PMID: [17433085](#) DOI: [10.1111/j.1743-6109.2007.00456.x](#)]
- 157 **Shoshany O**, Abhyankar N, Elyaguov J, Niederberger C. Efficacy of treatment with pseudoephedrine in men with retrograde ejaculation. *Andrology* 2017; **5**: 744-748 [PMID: [28380686](#) DOI: [10.1111/andr.12361](#)]
- 158 **Brooks ME**, Berezin M, Braf Z. Treatment of retrograde ejaculation with imipramine. *Urology* 1980; **15**: 353-355 [PMID: [7190335](#) DOI: [10.1016/0090-4295\(80\)90468-9](#)]
- 159 **Okada H**, Goda K, Koshida M, Kamidono S. Pregnancy by insemination of cryopreserved spermatozoa from a man with retrograde ejaculation: a case report. *J Reprod Med* 2004; **49**: 389-391 [PMID: [15214715](#)]
- 160 **Eppel SM**, Berzin M. Pregnancy following treatment of retrograde ejaculation with clomipramine hydrochloride. A report of 3 cases. *S Afr Med J* 1984; **66**: 889-891 [PMID: [6505897](#)]
- 161 **Hibi H**, Ohori T, Yamada Y. DPP-IV inhibitor may affect spermatogenesis. *Diabetes Res Clin Pract* 2011; **93**: e74-e75 [PMID: [21636156](#) DOI: [10.1016/j.diabres.2011.04.022](#)]
- 162 **Templeton A**, Mortimer D. Successful circumvention of retrograde ejaculation in an infertile diabetic man. Case report. *Br J Obstet Gynaecol* 1982; **89**: 1064-1065 [PMID: [7171519](#) DOI: [10.1111/j.1471-0528.1982.tb04668.x](#)]
- 163 **Brassesco M**, Viscasillas P, Burrell L, Calaf J, Rajmil O, Pomerol Serra JM, Morer Fargas F. Sperm recuperation and cervical insemination in retrograde ejaculation. *Fertil Steril* 1988; **49**: 923-925 [PMID: [3360184](#) DOI: [10.1016/s0015-0282\(16\)59909-9](#)]
- 164 **Shangold GA**, Cantor B, Schreiber JR. Treatment of infertility due to retrograde ejaculation: a simple, cost-effective method. *Fertil Steril* 1990; **54**: 175-177 [PMID: [2358086](#) DOI: [10.1016/s0015-0282\(16\)53660-7](#)]
- 165 **Hotchkiss RS**, Pinto AB, Kleegman S. Artificial insemination with semen recovered from the bladder. *Fertil Steril* 1954; **6**: 37-42 [PMID: [13220644](#) DOI: [10.1016/s0015-0282\(16\)31863-5](#)]
- 166 **Palermo GD**, O'Neill CL, Chow S, Cheung S, Parrella A, Pereira N, Rosenwaks Z. Intracytoplasmic sperm injection: state of the art in humans. *Reproduction* 2017; **154**: F93-F110 [PMID: [29158352](#) DOI: [10.1530/REP-17-0374](#)]
- 167 **Philippon M**, Karsenty G, Bernuz B, Courbiere B, Brue T, Saïas-Magnan J, Perrin J. Successful pregnancies and healthy live births using frozen-thawed sperm retrieved by a new modified Hotchkiss procedure in males with retrograde ejaculation: first case series. *Basic Clin Androl* 2015; **25**: 5 [PMID: [26034605](#) DOI: [10.1186/s12610-015-0021-4](#)]
- 168 **Liu X**, Gao M, Sun J, Sun Z, Song J, Xue X, Zhang Z, Shi J, Xing J. Effects of testicular sperm aspiration upon first cycle ICSI-ET for type 2 diabetic male patients. *Syst Biol Reprod Med* 2020; **66**: 355-363 [PMID: [32717167](#) DOI: [10.1080/19396368.2020.1785042](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

