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Genitourinary Complications In *Diabetes Mellitus*: A Review

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ABSTRACT

Urogenital complications are commonly found in patients with long standing diabetes mellitus. In the vast majority of patients, Diabetic neuropathy and/or angiopathy are the etiologies or most marked co-etiologies of micturition or sexual dysfunctions. As the deterioration of bladder retention and emptying as well as the erectile and ejaculatory dysfunction may have severe organic and psychosocial outcome, their existence (often unclear to the patient) should be thoroughly screened for in the routine diabetic clinic. Given hints of existence, thorough evaluation of the impaired organ system is mandatory. A wide range of various treatment modalities is available and can be individually offered following appropriate diagnosis.

Keywords: Bladder dysfunction; Cystopathy; Erectile dysfunction; Female sexual dysfunction; Diabetic neuropathy

1. INTRODUCTION

Dysfunction in bladder emptying and/or retention is often asymptomatic to the patient, especially in the beginning of this diabetic complication. On the other hand, sexual dysfunctions are readily professed by the patient. Sexual dysfunctions as erectile or ejaculatory dysfunction and infertility are commonly found in the male diabetic compared with the non-diabetic population. Even though these sexual dysfunctions often exert a dramatic negative impact on psychosocial living and self esteem of the patients with diabetes, they remain unappreciated in many instances. They do not attract medical attention and thereby possible treatment either owing to the embarrassment of the patient or to unawareness or negligence of the problem by the clinician. As the dysfunction of bladder storage and emptying as well as sexual dysfunction may have severe organic and psychosocial outcome, their existence (often unclear to the patient) should be thoroughly screened for in the routine diabetes clinic. Given hints of existence, detailed evaluation of the impaired organ system is mandatory. A wide range of various treatment approaches is available and can be individually offered after proper diagnosis [1].

2. MATERIAL AND METHODS

Exploration of published articles related with Genitourinary Complications in *Diabetes mellitus* was conducted and abstracts and full articles were included for the preparation of this review from online basis. The databases utilized for obtaining information are scientific research publications from journals indexed/available through PubMed, Scopus, and Google Scholar, Science Direct etc. Relevant facts were also obtained from general databases such as Google from a library source (Regional Research Institute of Unani Medicine, Srinagar).

3. OBSERVATIONS

3.1 Bladder Dysfunction

3.1.1 Physiology of Micturition

In adults, retention capacity of the urinary bladder is 300–600 ml. Until the final volume is reached only a minimal intravesical pressure increase is noticed and involuntary spinal reflexes avoid uninhibited contractions. During the filling phase, afferent impulses from the bladder are suppressed both by intraspinal and cerebral mechanisms; In addition, the sphincter apparatus is activated. When the maximal retention capacity is being reached, afferent impulses transmit this information to the conscience level. Then efferent motor activity from the pontine micturition center through the nuclei intermediolaterales of the spinal micturition centers at the level of T_{10}–L_2 and $S_{2–4}$ initiate the micturition. These nerve impulses are conducted to the secondary cholinergic neuron within the pelvic plexus. Peripherally, micturation is initiated by relaxation of the extrinsic striated sphincteric muscle and contraction of the smooth muscles of the bladder wall. In the lack of relevant anatomical subvesical obstruction, complete bladder emptying occurs in the presence of rather low intravesical pressures [1]**.**

3.1.2 Pathophysiology and Clinical Symptomatology of the Diabetic Bladder

In animal studies, rats with experimentally induced diabetes mellitus, micturition disorders start with degeneration of the afferent myelinated fibers [2]**.** Neurogenically mediated bladder contraction is altered in the diabetic rats, which explains an increased response to electrical field stimulation and a reduced cholinergic response. Though, the purinergic response does not appear to be altered, whereas remaining nonadrenergic–noncholinergic (NANC) component of contractile response of unknown origin is increased [3]**.**

Diabetes-induced decreases the contractility of bladder wall smooth muscle in rabbits has been related to an increased expression of thin filament proteins, calponin, tropomyosin, and caldesmon, which might change the contractile and cytoskeletal structure in bladder myocytes. The over expression of these thin filament associated proteins, which suppresses actin–myosin interaction and actomyosin adenosine triphosphatase, and the augmentation of this suppression by tropomyosin are likely to have an effect on the association between force and myosin light chain phosphorylation. Thus, needs higher levels of phosphorylation in diabetic detrusor compared with that of control. The subsequent effects of hyperglycaemia (e.g., oxidative stress) appear to modulate the transcriptional regulation of thin filament mediated regulatory proteins in bladder smooth muscle [4]**.**

In man, “diabetic bladder” illustrates a syndrome of reduced responsiveness of bladder filling, followed by increased bladder retention capacity and decreased bladder contractility. The decrease of sensation of a filled bladder (caused by the degeneration of the afferent myelinated fibers) is rapidly followed by degeneration of the non-myelinated efferent fibers resulting with detrusor hypocontractility. This hypocontractility translates clinically into reduced urinary flow, incomplete bladder emptying, and recurrent urinary tract infections and, as end stage renal disease, into bladder desensitization and acontractility with overflow incontinence. On the other hand to this classical situation of a diabetic bladder, autonomic neuropathy may cause irritative symptoms as urge, frequent urination, nocturia, or incontinence in the presence of other urological diseases [5-7].

3.2 Bladder Dysfunction in Women with Diabetes

It has been evaluated that urinary incontinence may affect nearly 50% of middle aged and older women, leading to major distress, restriction in daily activity, and poor quality of life. Diabetes mellitus is related with an increased risk of incontinence by 30–100%. It has been suggested that interventions that prevent or delay onset of diabetes may also prevent urinary incontinence. In the diabetes prevention program the prevalence of weekly stress incontinence was decreased by the diabetes prevention program intensive lifestyle intervention. Reducing incontinence may be an influential motivator for women with impaired glucose tolerance to prefer lifestyle modification to prevent diabetes. Large studies have recognized urge incontinence, an involuntary loss of urine with a feeling of urgency, as increased among women with diabetes, whereas there was no increased risk for stress incontinence, an involuntary loss of urine with physical activity [8]. Women with diabetes treated with insulin are at significantly higher risk of urge incontinence than those treated with oral hypoglycaemic agents or diet. However, how diabetes may contribute to the incidence or severity of urinary incontinence is not clearly understood [9].

3.3 Bladder Dysfunction in Men with Diabetes

Lower urinary tract symptoms (LUTS) are frequent, age-related complaints that are often accredited to benign prostatic hyperplasia (BPH). LUTS and BPH increases dramatically with age starting at about 50 years. Urinary straining, intermittency, post void dribbling and weak flow may signify urethral obstruction from BPH. However, among men with diabetes, related symptoms may also result from bladder dysfunction because of denervation and poor detrusor contractility. Other multifaceted associations of LUTS and BPH among men with diabetes include symptoms of urgency, frequency, and nocturia that may occur from detrusor over activity resulting from BPH, and/or microvascular complications related with diabetes, increasing hyperactivity of the detrusor. Because previous studies have failed to differentiate LUTS from BPH in men with diabetes, the effect of diabetes on the development or presence of LUTS and BPH remains questionable [8]. Recent studies suggest that LUTS may occur more commonly among men with diabetes, with an approximate 25% to nearly twofold increased risk of LUTS in men with diabetes mellitus. In addition, among men with BPH, diabetes is related with more LUTS symptoms compared with men without diabetes [8]. Experimental studies suggest that early changes in sodium and potassium channels occur in both BPH and diabetes similar to neuropathic models. These changes trigger altered excitability, leading to detrusor over activity and urinary frequency, progressively impaired contractility because of a myopathy can lead to incomplete emptying. Thus, a combination of numerous factors with differing time courses lead to LUTS and known urodynamic findings, making discerning an etiology and distinguishing classic diabetic cystopathy from neural plasticity additional obstruction because of BPH problematic [8].

3.3.1 Diagnostic Approach to Micturition Disturbances

In 40–80% of urologically asymptomatic patients with diabetes mellitus, abnormal findings were obtained in a comprehensive urodynamic work up. Many of these patients were aware of their abnormal micturition patterns only in structured inquiring. However, these often asymptomatic micturition disorders may have deleterious consequences for the upper urinary tract with significant renal impairment or even end stage renal disease. This low incidence of symptoms in the presence of possible severe outcome necessitates the inclusion of specific questions regarding micturition patterns in the yearly routine diabetic checkup. Here, frequency, sensation of incomplete bladder emptying, urinary tract infection, urgency, dysuria, nocturia, incontinence and need to use abdominal strain to empty the bladder should be specifically treated. In uncertain circumstances, a micturition protocol for three consecutive days and nights may be useful. A urinary lab completes the routine urinary bladder function test [1]**.** Given remembered hints for micturation disorders or recurrent urinary tract infection, a non-invasive urological work up consisting an uroflometry and a post void ultrasound of the bladder should be done. A detailed urological work up with proper urodynamics and radiological imaging of the urinary tract is needed in the presence of recurrent urinary tract infection or abnormal non-invasive findings. Endoscopic diagnostic procedures will be instituted according to the findings of the earlier mentioned diagnostics [10].

3.3.2 Therapeutic Options for Micturition Disturbances

The need for treatment of micturition disturbances is determined by the subjective and objective parameters of the impairment, by its etiology, its urological (non-diabetic) co morbidities and its secondary negative impact on the upper urinary tract as well as by the manual capacities of the patient. Although autonomic neuropathy is the most common cause for voiding dysfunctions in a patient with diabetes mellitus, other cofactors such as hormone deficiency, obstructive prostatic hyperplasia, or urethral and meatal stenosis may play a key role and must be taken care of when treatment options are considered and discussed with the patient. To determine these individual variables, the earlier mentioned rationalized urological approach is compulsory before treatment. The majority of diabetic voiding dysfunctions can be safely managed by conservative approaches. However, routine follow-up of the patient might be essential for early detection of treatment failures and avoidance of secondary complications [1].

Management of a large capacity bladder might begin with regular voiding intervals (during daytime, three hourly intervals are often appropriate). In addition, the patient is advised to take his time to void and to try to relax his pelvic floor muscles during micturition. A hypo- or even acontractile urinary bladder may help from parasympathomimetics (cholinergic drugs). In the existence of a mild-to-moderate infravesical prostatic obstruction, an alpha blocking agent can also be advised. If recurrent urinary tract infection is present inspite of these therapies and postvoid residual urine is more than 100 ml, either clean intermittent self-catheterization (4–5 times daily) should be done or a suprapubic catheter be put. Surgical reduction of the bladder's capacity has not been doing well in the past; the capability of neuromodulation or neurostimulation to restore bladder emptying in these patients (in the presence of autonomic neuropathy) also seems very restricted [10–13].

Anatomical infravesical obstruction is mainly seen in elderly male patients, though urethral strictures are a common cause of recurrent urinary tract infection in females. In case of a marked bladder outlet obstruction by benign prostatic hyperplasia, ablative procedures (transurethral resection of prostate, laser evaporization, thermoablation and open surgery) should be suggested. Urethral or meatal strictures permits endoscopic or formal repair [14].

3.4 Erectile Dysfunction in Diabetics

Erectile dysfunction, defined as the consistent or recurrent incapability of a man to attain and/or maintain a penile erection enough for sexual activity [15], is one of the most common sexual dysfunctions in men. Erectile dysfunction is more common with advancing age, and since the aged population will increase, its prevalence will continue to mount [16].

Diabetes mellitus is the most common organic cause for erectile dysfunction, the onset of which begins about 15 years prior in the diabetic than in the non-diabetic population. In the Massachusetts Male Aging Study (MMAS), the age-adjusted prevalence of minimal, moderate, or complete Erectile dysfunction was 17, 25, and 10% among 1238 men without diabetes and 8, 30, and 25% among 52 treated men with diabetes, correspondingly [17]. Thus, even though the sample size of diabetic subjects in the MMAS was small, this population based study showed an increased prevalence particularly of complete erectile dysfunction among men with diabetes. The Cologne Male Survey the prevalence of erectile dysfunction was threefold increased, reaching 60% among men with diabetes compared with only 19% in the general population [18].

3.4.1 Physiology and Pathophysiology

Penile erection is a neurovascular event modulated by psychological factors and hormonal status depending on suitable trabecular smooth muscle and arterial relaxation in the corpus cavernosum. On sexual arousal, nerve impulses cause the release of cholinergic and non-noradreergic, non-cholinergic (NANC) neurotransmitters that mediate erectile function by relaxing the smooth muscle of the corpus cavernosum. A main neural mediator of erection is nitric oxide (NO), which activates guanil cyclase to form intracellular cyclic guanosine monophosphate (GMP), a powerful second messenger for smooth muscle relaxation. Cyclic GMP in turn activates a specific protein kinase, which phosphorylates certain proteins and ion channels, resulting in a fall of cytosolic calcium concentrations and relaxation of the smooth muscle. When the flaccid state returns, cyclic GMP is hydrolyzed GMP by phosphodiesterase (PDE) type 5. In the corpus cavernosum four PDE isoforms

have been identified (types 2–5), but PDE 5 is the chief isoform, while the others do not appear to have a significant role in erection [19].
The pathogenesis of erectile dysfunction in diabetes is thought to be multifactorial as it may be related to neuropathy, accelerated atherosclerosis, and alterations in the corporal erectile tissue. Such changes may include smooth muscle degeneration, abnormal collagen deposition, and endothelial cell dysfunction [20]. If irreversible, these corporal degenerative changes can restricts the achievement of any pharmacotherapy. Advanced glycation end products have been shown to quench NO and to be elevated in human diabetic penile tissue. It has been hypothesized that advanced glycation end products may mediate erectile dysfunction through upregulation of inducible nitric oxide synthase and down regulation of endothelial NOS (eNOS) [21]. In addition, protein kinase C activation by diabetes may reduce NOS activity [22].

3.4.2 Diagnosis

A good clinical history and physical examination are the fundamentals of evaluation. It is imperative to set up the nature of the erectile problem and to differentiate it from other forms of sexual complexity, such as penile curvature or premature ejaculation. An interview with the partner is advisable and will verify the problem, but might also reveal other causes of the difficulties like vaginal dryness. The importance of psychological and organic factors may be determined from the clinical history. Drugs which may be associated with erectile dysfunction include tranquillizers (phenothiazines, benzodiazepines), antidepressants (tricyclics, selective serotonin reuptake inhibitors), and antihypertensive (β-blockers, vasodilators, central sympathomimetics, ganglion blockers, diuretics, ACE inhibitors) [23]. In most patients advanced investigation is not indicated. A comprehensive history is most important, and for many patients examination can be limited to the regular monitoring of diabetes mellitus and its risk factors and complications as well as examination of the genitalia. Patients should be educated about the advantages and disadvantages of each treatment and given advice on treatment outcome and ease of use [24].

3.4.3 Management

The early management should be to advise the patient to reduce possible risk factors and to optimize glycemic control. However, no studies are available to show that improvement in glycemic control will exert an encouraging effect on erectile dysfunction. In fact, a recent study could not demonstrate an effect of intensive diabetes therapy maintained for 2 years on erectile dysfunction in men with type 2 diabetes *(25)*. Healthy lifestyle factors are related with maintenance of erectile function in men. A randomised controlled study recently evaluated the effect of weight loss and increased physical activity on erectile and endothelial functions in obese men. Men randomly allocated to the intervention group received detailed advice about how to achieve a loss of 10% or more in their total body weight by reducing caloric intake and increasing their level of physical activity. Men in the control group were given general information about healthy food options and exercise. After two years the statistical analysis showed mean international index of erectile function (IIEF) score bettered in the intervention group from 13.9 to 17 points, but not in the control group. In multivariate analyses, changes in body-mass index, physical activity and C-reactive protein were independently associated with changes in IIEF score. Thus, lifestyle changes are associated with improvement in sexual function in obese men with erectile dysfunction Even if the cause is organic; almost all men with erectile dysfunction will be affected psychologically. Sexual counselling is a vital aspect of any treatment, and it is preferable to also involve the partner. Phosphodiesterase 5 inhibitors like Sildenafil, Vardenafil, Tadalafil are Peripheral conditioners used in erectile dysfunction [26].

3.5 Other Sexual Problems In Men With Diabetes

Diminished or absent testicular pain has been reported as an early sign of autonomic neuropathy. Retrograde ejaculation from the prostatic urethra into the bladder might occur rarely and follows loss of sympathetic innervations of the internal sphincter, which normally contracts during ejaculation. Complete loss of ejaculation may indicate extensive pelvic sympathetic involvement and like retrograde ejaculation, causes infertility, which may be treated by insemination [27].

3.6 Female Sexual Dysfunction

Female sexual dysfunctions include continual or recurrent disorders of sexual interest/desire, disorders of subjective and genital arousal, orgasm disorder, pain and difficulty with attempted or completed intercourse. The technical knowledge on sexual dysfunction in women with diabetes is rudimentary. Sexual dysfunction was observed in 27% of women with type 1 diabetes. Female sexual dysfunction was not linked to age, BMI, HbA_1c, duration of diabetes, and diabetic complications. However, female sexual dysfunction was related to depression and the quality of the partner relationship [28]. Recently, the prevalence of female sexual dysfunctions in premenopausal women with the metabolic syndrome was compared with the general female population. Women with the metabolic syndrome had decreased mean full female sexual function index score, reduced satisfaction rate, and higher circulating levels of C-reactive protein (CRP). There was an inverse relation between CRP levels and female sexual function index score [29]. Difficulties affecting sexuality in women with diabetes are fatigue, changes in perimenstrual blood glucose control, vaginitis, decreased sexual desire, decreased vaginal lubrication, and an increased time to reach orgasm. Few episodes of depression which is twice more common than in men can lead to a loss of libido. To which degree these symptoms are related to autonomic neuropathy has also been examined in a few studies, the results of which are at dissent [30]. The clinical examination for women with diabetes with sexual dysfunction should include the duration of symptoms, psychological state, concomitant, medications, presence of vaginitis, cystitis and other infections, frequency of intercourse, blood pressure, BMI, pelvic examination, presence of discharge and glycemic control [31].

4. Conclusion

Diabetes mellitus is slowly emerging as a major public health challenge globally. Though the organ system complications inflicted by poor glycemic control are well understood. Diabetes mellitus induced lower urinary tract dysfunction is poorly defined ad understudied. However, clinical and experimental studies have prove beyond any shadow of doubt that long term uncontrolled hyperglycaemic state brings about structural and functional changes in kidneys, urinary bladder and urethra, contributing to worsening of lower urinary tract coordinated function . The clinician and health care providers should be well aware of these lower urinary tract dysfunctions induced by diabetes mellitus to avoid potential morbidity that could have serious implications on the overall quality of life. Therefore strict glycemic control plays an important role in managing genitourinary disorders in people with diabetes mellitus.

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Conflict of Interest:

There is no conflict of interest.

Author Contributions and Guarantor Statement.

Zaffar Hussain researched data, contributed to discussion, and wrote the first draft of the manuscript. M.A. Kalam reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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