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STORAGE AND VOIDING DYSFUNCTIONS OF THE LOWER URINARY TRACT IN DIABETIC PATIENTS: MORE THAN A FEELING

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ABSTRACT

INTRODUCTION To evaluate the effects of insulin dependent diabetes mellitus type 2 (IDDM2) on the urinary bladder function in patients with lower urinary tract symptoms (LUTS) and to classify patients according to videourodynamic outcomes. **MATERIALS AND METHODS** We retrospectively analyzed 4435 videourodynamic examinations in 3850 patients from 07/2001 until 12/2012. We restricted patients to type 2 diabetics which were insulin dependent for at least one year. We excluded diabetics with neurological diseases in the medical history as well as previous surgeries. The following parameters were evaluated: micturition frequency at day- and nighttime, maximum voided volume, body-mass-index and videourodynamical diagnosis. Videourodynamics were performed according to the guidelines of the international continence society (ICS). **RESULTS:** With respect to the exclusion criteria we evaluated a total of 129 patients with IDDM2 remained (39 women, 90 men). Patient characteristics and subjective parameters showed an elevated psychological strain based on pathological voiding habits resulting in a decreased quality of life. Eight different videourodynamical diagnoses were confirmed despite the similar symptom complex. 50% of these patients showed a combined dysfunction of at least two different videourodynamical diagnoses. **CONCLUSIONS:** Patients with LUTS and IDDM2 present bothering symptoms. These symptoms result in a low quality of life, which underlines the necessity of a proper treatment regime. However, videourodynamics proved that there are differences in the diagnoses despite the similar symptom complex. Furthermore, treatment regimens have to get adapted in the case of combined dysfunctions. According to the specific type of bladder storage and voiding dysfunction individually tailored treatment is mandatory, even implicating treatment options indicated in one type, however, contraindicated in another type.

KEYWORD

Diabetes mellitus; diagnostic evaluation; urodynamics; urinary incontinence.

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INTRODUCTION:

Urological complications in diabetes mellitus (DM) are common, up to "66% of patients with diabetes report symptoms of voiding dysfunctions" 1-6. Despite this high relevance, an exact urodynamic classification of lower urinary tract symptoms (LUTS) due to diabetic neuropathy (DN) is still missing. Urodynamic abnormalities are described either as detrusor overactivity, underactivity or as acontractile detrusor, but "indeterminate findings" are still representing up to 10% of these findings 4, 7, 8. Possible combinations of different pathologies are not described at all.

Recently a multitude of experimental and clinical studies has provided deeper insights into the pathogenesis of diabetic neuropathies presenting a serious complication of DM 9,10,11. The severity and occurrence of clinically significant DN is considered to be correlated with the duration of DM with consecutively induced effects on small fibers of the nerves by serum insulin concentration 12, 13.

Two types of DN must be differentiated:

1. Somatic DN has to be subdivided in acute and chronic neuropathy. Acute neuropathy "is rare, it tends to follow periods of poor metabolic control or sudden changes in glycemic control and is characterized by the acute onset of severe sensory symptom." 1, 6

2. Autonomic DN of the urogenital tract may occur in various parts of the central and peripheral nervous system. Depending on the location and the extent of injury as well as possible combinations of the various central and peripheral nervous system, the onset and patterns of LUTS varies widely 14,15,16. The diagnosis of autonomic DN would be facilitated, if it would manifest primarily and exclusively in a single malfunction of the bladder.

The pathophysiology of diabetes-associated complications affecting the bladder can be due to different causes: Alterations in the detrusor smooth muscle, neuronal dysfunctions, and urothelial dysfunctions 17, 18 as well as neurological impairment in DM has been related to axonal damage and demyelination at multiple locations, centrally and peripherically, mainly caused by chronic high levels of glucose 19. So, several parts of the autonomic nervous system can be involved leading to combined forms of bladder dysfunction. Furthermore, the impairment of the lower urinary tract can be complicated by secondary changes such as vesicoureteral reflux and post void residual (PVR) resulting from the initial pathology.

LUTS are one of the most common diabetes-related complications, affecting 50% to 66% of all patients with diabetes, individuals with both type 1 and type 2 diabetes can suffer from DN 1,20. However "future studies need to take as much care as possible to delineate each condition and to examine each of the underlying pathways before we are able to better understand how diabetes affects benign prostate hyperplasia (BPH) and LUTS" 20.

Unfortunately, guidelines such as those of the American Diabetes Association (ADA) or National Institute for Health and Care Excellence (NICE) inadequately address the issue of LUTS because neither the urodynamic diagnostic approach nor treatment options are considered properly 1, 6, 20.

In this study we reviewed over 10 years of videourodynamics to aware colleagues for the variability of storage and voiding dysfunctions resulting from diabetes.

MATERIAL AND METHODS:

We retrospectively evaluated 4435 Videourodynamics in 3850 patients from July 2001 until December 2011.

Before the videourodynamical examination, all patients received a full urological checkup including medical history, bladder diary, urine test and sonography of the lower and upper urinary tract including trans rectal ultrasound in men, resulting in evaluation of the following subjective parameters: IPSS-, life quality index, micturition frequency during daytime and nighttime, maximum voided volume, body mass index.

The videourodynamic assessment was performed in a standardized matter in accordance to the guidelines of the international continence society (ICS) 21.

We included only patients with diabetes mellitus type 2 which were insulin-dependent for at least one year.

Other relevant urological diseases, such as BPH or urinary tract infections have been ruled out before by our diagnostic approach. Neurological diseases such as stroke or multiple sclerosis, possibly inducing LUTS had also been excluded by the medical history as well as neurological judgment. In case of uncertain findings, a previous neurological check was performed.

Data analysis:

All data were retrospectively evaluated. Relevant parameters were analyzed by descriptive statistics using SPSS 13.0.

RESULTS:

Patient population, characteristic:

We evaluated 129 patients with IDDM2 and no previous surgical approach, 39 women and 90 men. The characteristics of this population are presented in table 1.

There were no significant differences in any parameter observed between men and women. Major bothering symptoms were similar in nearly all patients:

1) increased urinary frequency, 2) nocturia and 3) urgency with and without incontinence resulting in an elevated IPSS as well as life quality index.

Furthermore, maximum voided volume trended to be decreased compared to regular findings.

Videourodynamical results:

With respect to the videourodynamic results, we observed eight different videourodynamical patterns. All diagnoses are listed in table 2. The changes in clinical findings which are caused by these pathologies are presented in table 3.

Furthermore, we observed combined storage and voiding dysfunction in a high percentage of the patient population. An example for a combined bladder dysfunction is the combination of bladder outlet obstruction and detrusor overactivity, or stress urinary incontinence with acontractile detrusor.

In men a second urodynamical diagnoses was present in 46/90 patients (51.1%), three urodynamical relevant diagnoses were observed in another 4/90 (4.4%).

In women a second urodynamical diagnoses was present in 15/39 patients (38.5%), three urodynamical relevant diagnoses were observed in another 4/39 (10.3%).

Table 1: Patient population, BMI = Body mass index, IPSS = international prostate symptom score, LQI = life quality index, TMF = Micturition frequency during daytime, NMF = Micturition frequency during nighttime, MVV = maximum voided volume

	Men (n=90)	Women (n=39)
Age (years)	65.6 (± 12.3)	64.4 (± 14.7)
BMI	29.9 (± 5.7)	29.2 (± 6.6)
IPSS	16.3 (± 7.0)	17.4 (± 6.0)
LQI	3.8 (± 1.6)	4.2 (± 1.3)
TMF	9.8 (± 5.9)	12.9 (± 11.8)
NMF	3.2 (± 1.9)	2.9 (± 2.2)
MVV (ml)	263.2 (± 174.3)	337.1 (± 207.6)

Table 2: Primary videourodynamic diagnoses

	Men (n=90)	Women (n=39)	Treatment options
Regular finding	1	1	X
Bladder outlet obstruction	20	2	Men: alpha-blockade, surgery Women: anatomical correction (functional obstruction)
Detrusor overactivity	54	15	anticholinergics, botulinumtoxin, b3-agonists
Bladder hypersensitivity	4	3	anticholinergics, botulinumtoxin, b3-agonists, biofeedback
Stress urinary incontinence	2	11	Physiotherapy, slings, artificial sphincter
Morphological changes, i.e. diverticula	4	0	Surgery
Acontractile detrusor	3	3	Bladder training, clean intermittent catherization, cholinergics (no evidence)
Detrusor dyscoordination (Fig. 1)	2	4	Alpha-blockade, deobstructive surgery
Combination of different patterns	50	19	Depends on the pathologies

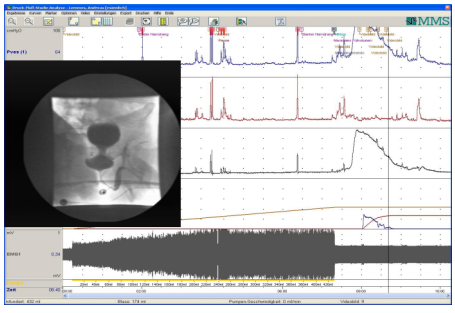
Table 3: Key changes in videourodynamical diagnoses

	Urodynamic pattern	Symptoms	MCC	Pmax	F	PVR	Mt
1	Regular finding	None					
2	Bladder outlet obstruction	urgency, nocturia, with or without incontinence					

3	Detrusor overactivity	urgency, nocturia, with or without incontinence					
4	Bladder hypersensitivity	urgency, with or without incontinence					
5	Stress urinary incontinence	(urgency), incontinence					
6	Morphological changes, i.e. diverticula	urgency, nocturia, with or without incontinence					
7	Acontractile detrusor	urgency, nocturia, with or without incontinence					
8	Detrusor dyscoordinatio n (Fig. 1)	urgency, nocturia, with or without incontinence					

Fig. 1:

Videourodynamical prove of detrusor dyscoordination in male patient with singular contraction of the medial part of the bladder, final voiding phase



DISCUSSION:

Clinical relevance:

LUTS is considered to be associated with urological disorders or obvious neurological etiologies (i.e. stroke, multiple sclerosis). Direct associations are suggested in DM, but final proof is still lacking. Subclinical DN resulting in LUTS can possibly occur on an early onset even before manifestating of DM, a correct diagnosis on time with early treatment is essential for LUTS to prevent further damages to the lower urinary tract as well as for other DM-related pathological consequences 1, 6.

Multivariant analyses identified DM as an important independent risk factor for urinary incontinence. Early interventions preventing or postponing the onset of DM may also prevent urinary incontinence 5. Unfortunately, urological effects of DM are not as well studied as effects on other organ systems. This is also due to the fact that neurogenic dysfunctions of visceral organs are difficult to diagnose objectively.

However, first symptoms of clinically relevant DN are often presented as LUTS. Two different pathways can be described: 1) DN, which results in neurological failures resulting in different urological complications, such as LUTS and erectile dysfunction 1, 6, 14, 15, 17, 18. 2) Vascular damages caused by DM, resulting in voiding dysfunction, BPH as well as erectile dysfunction.

If these vascular damages are also influencing the bladder function has not been proven yet. However diabetic angiopathy is also a possible cause of bladder dysfunction, either by direct influence of the smooth muscle by ischemia, or by possible neurogenic alteration such as mini-stroke caused by vascular damages 22, 23. Because the effect and clinical outcome of these alterations is still unknown, the urological assessment is of paramount importance. The data of this study proves the variety of damage caused by DN. By the appearance of DN on different location a forecast of the consecutive storage or voiding dysfunction is not possible, it also elevates the difficulty of proper diagnosing because the alterations are so varying that urologists have to anticipate all possible storage and voiding dysfunctions. We could observe these different alterations by diagnosing eight different videourodynamical results which also varies from morphological to functional changes in our study population. Already in 1985 scientific research in eleven diabetic patients identified different forms of storage and voiding dysfunction in the human bladder: 1) detrusor hyperreflexia and 2) detrusor hypo- or areflexia 14.

Noteworthy, clinical symptomatology was almost identical in all groups, encompassing urinary frequency, urgency, nocturia, in some cases with and in other cases without PVR. Only the assessment of the proposed urological diagnostic approach was able to detect major differences in bladder and voiding dysfunctions despite similar symptoms.

The importance of this proper diagnostic approach is highly relevant because LUTS in DM is still underestimated. Urologists reported that 81.1% of their diabetic patients were suffering of LUTS. General practitioners reported that still 60.7% of their diabetic patients showed symptoms of LUTS 24. These data are a plea for a regular and extensive urological check for diabetic patients, sometimes including minimal-invasive approaches comparable to other neurogenic bladder dysfunctions where urodynamics are recommended 25.

Morphological changes:

Possible alterations due to DN as well as vascular changes in DM are resulting in morphological changes which have been shown for BPH as well as erectile dysfunction 22, 23. Our patient population showed the possibility of other structural and morphological shifts as well. For women we could observe the appearance of stress urinary incontinence which is caused by intrinsic sphincter deficiency (ISD) or bladder neck hypermobility (BNH), both are structural weaknesses of either muscular tissue or connective tissue. Despite the tough challenge in diagnosing these pathologies by conventional urodynamics26,27 ,we could avoid this by the videourodynamic assessment which allows a categorization between BNH (closed bladder neck) and ISD (open bladder neck) by cystography. The discussion about the necessity of fluoroscopy during urodynamical assessment is ongoing 28, we think that it should be added where possible to elevate the quality of diagnostic. Possible fear against radiation exposure could get ruled out before 29.

However, despite outruling obvious bladder outlet obstruction(BOO) by sonography and cystoscopy we still observed BOO in 22 patients (20 men, 2 women). This fact proves that diagnosing these kinds of voiding dysfunction requires more than just imaging techniques. This underlines the importance of the urodynamical assessment.

Treatment modalities:

Therapeutic approaches only relying on symptoms would definitely allocate patients to a wrong treatment regime, in some cases even contraindicated ones.

For example, applying anticholinergics in detrusor overactivity is the gold standard; however, applying anticholinergics in acontractile detrusor would result in elevated post void residual urine and worsening of the

disease despite the similar symptom complex.In our opinion the most important aspect of this study is the high rate of combined storage and voiding dysfunctions. More than 50% of the patient population was diagnosed with at least 2 urodynamical relevant pathologies. These findings have not been addressed yet in DM.

The results showed a variety of different combinations. However, we cannot recognize typical patterns from our data which could help to forecast certain combinations.

More importantly a proper diagnostic approach is essential to provide a successful treatment.

Treatment options to the different urodynamical pathologies are illustrated in table 2.

Limitations and drawbacks:

This study shows the wide variety of pathological effects of DM on the lower urinary tract, resulting in different forms of storage and voiding dysfunction caused.

However, several drawbacks must be considered:

1) The retrospective character: Despite of the retrospective character, these results elevate the insight of the effect of DM on the lower urinary tract.The videourodynamic assessments were upraised in a high-volume center with more than 350 videourodynamics per year. The standardized procedure in accordance to the ICS as well as the long-time expertise as neurourological department improves the quality. Furthermore, these data, allocated in clinical procedures, are showing its practical relevance, which can be replicated in other institutions.

By the strict exclusion criteria, it can be supposed that the data is representative for the effect of IDDM2 on the lower urinary tract.

2) Key parameters for DM, such as HbA1c were not evaluated: We started the evaluation in 2001, HbA1c became a routine parameter in 2009. Furthermore, the literature has no prove yet for a direct link between HbA1c and the intensity of DN 1, 6.

3) We propose the new term "detrusor dyscoordination", which has not been defined yet in the literature. It is a description of a bladder dysfunction, diagnosed by reproducible morphological changes during voiding as seen in figures 1 . Unfortunately, the ICS has not integrated morphological changes in its respective standardization papers 30.The issue about the necessity of the combination of fluoroscopy and urodynamic assessment is a hot topic and gets discussed extensively 28. Therefore, we plea for the importance of videourodynamics as an integral diagnostic procedure, emphasizing the necessity of evaluating morphological changes, which can also be the only changes in DN, i.e. in prostate hyperplasia 22, 23.

4) Our series does not distinguish whether NDO was solitary due to DM or possibly induced by age. An acknowledged approach would be the differentiation between terminal and phasic detrusor overactivity. However, reference literature 8 did not differentiate these two types of overactivity. In future studies it should get investigated further by comparing young vs. old diabetic patients with LUTS. Our analysis of urodynamic tracings showed that both patterns occur, giving a hint that definitely other factors beyond age contribute to these effects. However, we only had 6 patients below 40 years of age, so it is not possible to see a trend or significant differences in their respective parameters.

Conclusion

In conclusion, our results are a strong and convincing plea for an extended diagnostic approach in the assessment of patients with DM and concomitant complicated LUTS. It should incorporate ultrasound, cystoscopy and videourodynamics in cases in which organic etiologies have been excluded already. This is necessary, because clinical symptoms of LUTS in DM do not reflect the underlying pathophysiology. The presence of urgency, slow stream and post void residual urine is possible in a big variety of storage and voiding dysfunction resulting in the necessity of different, sometimes even contrary treatment approaches. For a precise differentiation and subtyping of the various forms of bladder dysfunction an interdisciplinary collaboration between internal medicine, urology, neurology and gynecology is not only beneficial but must be considered as mandatory: An early diagnosis of DN, treatment initiated in time and individualized according to the proposed groups can prevent progression of the individual patient.

Abbreviations:

Key definition for abbreviations: LUTS = lower urinary tract syndrome; DM = Diabetes mellitus; DN = Diabetic neuropathy; PVR = post void residual; IDDM2 = insulin dependent diabetes mellitus type 2; BPH = benign prostate hyperplasiae, NDO = neurogenic detrusor overactivity, ICS = international continence society, ADA = American Diabetes Association, NICE = National Institute for Health and Care Excellence

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