Impact of diabetes mellitus on urinary continence after holmium laser enucleation of the prostate due to lower urinary tract symptoms: a retrospective study

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Introduction Diabetes mellitus (DM) is known as a risk factor of stress urinary incontinence after Holmium laser enucleation of the prostate (HoLEP). We aimed to compare the postoperative continence status of patients with and without DM, after HoLEP surgery.
Material and methods A total of 214 patients who underwent HoLEP between January 2017 and January 2020 were retrospectively assessed. Functional outcomes, perioperative total operation time (TOT) (min), enucleation time (ET)(min), enucleation efficiency (EE)(g/min), enucleated tissue weight (ETW)(g), morcellation efficiency (ME)(g/min), morcellation time (MT)(min), continence status, intraoperative and postoperative complications according to Clavien–Dindo classification were recorded.
Results A total of 96 patients had DM additional to benign prostate hyperplasia (BPH) (Group 1), while 118 patients had only benign prostate hyperplasia without DM (Group 2). When comparing preoperative and postoperative functional outcomes, a statistically significant improvement was observed in both groups from baseline to the 1st and 6th month follow-up (p ≤0.001). There were no statistically significant differences between groups in postoperative stress urinary incontinence at postoperative months 1 and 6 (1.7% vs 2.1% , p = 1 and 0.8% vs 1%, p = 1 ; respectively). There was no significant difference between groups in intraoperative and postoperative complications (p >0.05).
Conclusions HoLEP is safe to perform in patients with DM at low complication and urinary incontinence rates.

Key Words: benign prostate hyperplasia ‹› diabetes mellitus ‹› enucleation
‹› holmium laser enucleation of the prostate ‹› stress urinary incontinence

INTRODUCTION

Holmium laser enucleation of the prostate (HoLEP) has become an increasingly popular minimally invasive surgical prostate intervention over the past 20 years since it was first described in 1998 [1]. It is an alternative to transurethral resection of the prostate (TURP) and open prostatectomy (OP) in terms of efficacy, safe-ty, and complications [2–6]. Despite HoLEP's advantages, postoperative stress urinary incontinence (SUI) continues to be a major problem after surgery, strongly affecting the patients` quality of life (QoL) [7, 8]. Various risks of SUI are considered relevant after HoLEP such as the patient comorbidities; neurologic diseases, diabetes mellitus (DM), large prostate volume, the surgeon's experience and operation time

[9–13]. According to the literature, of those risks, surgeon's experience and DM were found to be the main predictive factors in terms of SUI after HoLEP [14]. DM can demonstrate its main effect by damaging the autonomic and somatic nerves that stimulate the bladder, bladder neck, and external urethral sphincter (EUS), delaying wound healing [9]. Although DM is known to be a risk factor for urinary incontinence after HoLEP, there are few studies on HoLEP's effectiveness on postoperative continence in DM patients with BPH.

With this perspective, we aimed in this retrospective study to compare postoperative continence status of patients with and without DM after HoLEP.

MATERIAL AND METHODS

Patient selection

After institutional review board approval (ID: 2020-15/3), the data on 538 patients who underwent HoLEP between January 2017 and January 2020 were determined retrospectively. A signed informed consent form was obtained from the patients. Patients' age (years), prostate-specific antigen (PSA) (ng/mL), preoperative and postoperative hemoglobin (Hb) levels (g/dL), Hb drop and preoperative parameters including prostate volume (mL) in transabdominal ultrasonography, International Prostate Symptom Score total (IPSS-Total), maximum urinary flow rate (Qmax) (mL/s), post voiding residual volume (PVR) (mL), comorbidities and medications used were recorded. Patients were asked to come for follow-up examinations at the 1st and 6th post-operative months and IPSS scores, Qmax and continence statuses were recorded. Continence status was evaluated with respect to the standards proposed by the International Continence Society (ICS) [15]. Consequently, all patients were questioned in terms of any leak because of exertion, effort, sneezing or coughing. Any urine leak was considered positive regarding SUI. Total urinary control was classified as no SUI. Urge UI (UUI) was defined as involuntary leakage preceded immediately by urgency. Complete dryness was considered as continence. All patients received a 5-alpha reductase inhibitor or/and an alpha-blocker drug at least 6 months before the surgery. For DM patients, urodynamic testing was performed when a neurogenic bladder was suspected, i.e., in case of high post-void residual and overflow incontinence. All patients were questioned about taking an oral antidiabetic and/or insulin for DM treatment. The inclusion criteria for HoLEP surgery were the patients not benefiting from medical treatment or whose medication had been discontinued because of side effects (alpha-blocker and/or 5-alpha reductase inhibitor) with

IPSS-T ≥8, Qmax ≤15 mL/s and PVR ≥50 mL, a history of recurring or refractory urinary retention and bladder stones, and taking oral antidiabetics and/or insulin for DM treatment. Excluded were 10 patients with a history of pelvic, bladder, prostate or rectum surgery, pelvic trauma, pelvic radiotherapy; 8 patients with a neurogenic bladder due to diabetic neuropathy or other neurologic pathologies; 118 patients with any additional comorbidity except DM; 39 patients with less than a 6-month follow-up, and 49 patients with missing data. We also aimed to evaluate the efficiency of the HoLEP technique [16]. We therefore also excluded 100 standard-technique enucleations (Gilling`s). Total operation time (TOT; min), enucleation time (ET; min), enucleation efficiency (EE; g/min), enucleated tissue weight (ETW; g), morcellation efficiency (ME; g/min), morcellation time (MT; min), laser energy used (Joule) used, laser efficiency (LE; Joule/g), catheterization time (CT; hour), hospitalization time (HT; hour), intraoperative and postoperative complications with respect to modified Clavien–Dindo classification, and their management were documented [17].

Surgical equipment and surgical technique used

A 26-Fr continuous flow resectoscope, a laser-fiber stabilizing bridge, 120 W Holmium laser (VersaPulse; Lumenis Inc., Israel), a 550-μm end-firing laser fiber (SlimLine; Lumenis Inc.), and a 26-Fr nephroscope were used in all patients. A Lumenis VersacutTM (Versapulse; Lumenis Inc., USA) and Hawk (Hanghzhou Hawk Optical Inst. Co., China) morcellators were used to morcellate. All surgeries included in this study were performed via the 'Omega Sign' technique as described [16]. The procedures were performed by a single surgeon (LT) who has experience [18] over 700 HoLEP interventions.

Statistical analysis

The Statistical Package for Social Sciences 23.0 software (SPSS 23.0, Chicago, IL, USA) was utilized. The Kolmogorov-Smirnov, Kurtosis, and Skewness Tests were used to assess the normality distribution. The clinical characteristics of two groups were compared with Mann Whitney U or Student t-test for continuous variables. For categorical variables, Fisher's Exact test or Pearson Chi-Square test were used. All statistical tests were two-sided, with p <0.05 considered as statistically significant.

RESULTS

A total of 214 patients were included in this study. There were 96 of 214 which were the patients with

DM additional to BPH (Group 1) and 118 patients who diagnosed with only BPH without DM (Group 2). Baseline characteristics and preoperative data on the groups are shown in Table 1. Except for preoperative Hb levels, the patients' age (year), preoperative parameters such as PSA (ng/mL), prostate volume (mL), IPSS-Total, Qmax (mL/s), and PVR (mL) were similar between groups (Table 1) (p >0.05). Perioperative data on the groups are shown in Table 2. Except for the Hb difference between preoperative and postoperative Hb levels, there were no statistically significant differences between groups (p >0.05) in TOT, ET, EE, ETW, ME, MT, laser energy used, LE, CT, and HT.

Table 1. *Baseline characteristics and preoperative data on study groups*

Parameters	Group 1 (N: 118)	Group 2 (N: 96)	P Value
Patient age (year)	67 ±8.01	65 ±8.45	0.18
PSA (ng/ml)	5.38 ±4.89	5.2 ±3.75	0.14
Hb level (g/dL)	13.45 ±1.06	13.9 ±1.31	**0.046***
Prostate volume (ml)	96 ±52.81	93.5 ±47.11	0.36
IPSS Total	29 ±3.53	30 ±3.46	0.33
Qmax (ml/s)	8 ±4.96	9 ±4.42	0.13
Q ave (ml/s)	4 ±2.12	4.2 ±1.68	0.08
PVR (ml)	158 ±138.29	149.5 ±140.68	0.64

N – number of patients; IPSS – International Prostate Symptom Score; QoL – Quality of Life; PVR – post voiding residual volume; Hb – hemoglobin; Qmax – maximum flow rate; Qave – average flow rate; PSA – prostate-specific antigen; *Values in bold statistically significantly different. P <0.05.

Table 2. *Perioperative group data*

Parameters	Group 1 (N: 118)	Group 2 (N: 96)	P Value
Enucleation time	55 ±29.76	59 ±33.49	0.41
Enucleation efficiency	1.13 ±0.53	1.11 ±1.05	0.31
Enucleation weight	70 ±42.78	66 ±38.69	0.69
Morcellation time	8 ±11.19	7 ±6.87	0.68
Morcellation efficiency	8.21 ±4.14	8.81 ±5.63	0.89
Laser energy used	73 ±93.18	71.5 ±41.45	0.92
Laser efficiency	1.2 ±0.97	1.13 ±0.85	0.89
Total operation time (minute)	65 ±33.04	66 ±36.46	0.76
Hospitalization time (hour)	28 ±11.26	28 ±7.94	0.79
Catheterization time (hour)	24 ±13.84	26 ±19.61	0.29
Postoperative Hb (g/dL)	13.3 ±1.09	13.05 ±1.09	0.11
Hb difference between preoperative and postoperative Hb levels (g/dL)	0.2 ±0.25	0.2 ±1.15	0.07

N – number of patients; Hb – hemoglobin
Statistically analysed with Mann Whitney U test

Comparisons of baseline and postoperative 1st and 6th month follow-up data and the patients' continence status are shown in Table 3. When comparing preoperative and postoperative functional outcomes ,we noted a statistically significant improvement in both groups from baseline to 1st and 6th month follow-up (p <0.001). SUI was observed in two patients (2.08%) and UUI in two patients (2.08%) in both groups, postoperatively at the 1st month. SUI was observed in one patient (1.04%) in both groups, whereas no patient had UUI postoperatively at the 6th month follow-up, there was no statistically significant difference between groups in postoperative incontinence status (p >0.05) (Table 3). Intraoperative and postoperative complications in both groups are given in Table 4. There was no significant difference (p >0.05) in intraoperative and postoperative complications, and no patient required blood transfusion. There were no cases of intraperitoneal or extraperitoneal bladder perforation, no device problem or malfunction in either group. One patient (1.04%) in each group was given an intravenous antibiotic during the postoperative period for a urinary tract infection (p >0.05). One patient in each group underwent clot evacuation using a urethral catheter managed with irrigation (1.04%). Another patient in Group 1 only needed a cystoscopic clot evacuation (1.04%), here there was also no significant group difference (p >0.05). We observed a bladder neck contracture (n = 1) and meatal stenosis (n = 1) in Group 2 only; there was no significant difference between groups (p >0.05). Urethral stricture was observed in 1 patient (1.04%) in Group 1 and managed by internal urethrotomy, while no Group 2 patient had that complication (p >0.05). Re-catheterization was not required in either group.

DISCUSSION

Diabetes mellitus is a disease that can affect the bladder nerves involved in the urethral sphincter and urination functions. In an animal study, DM was shown to impair the striated and smooth muscles muscles in the urethra [19]. DM impairs external urethral sphincter (EUS) phasic activity and the coordination of urethral smooth muscle relaxation, and involuntary contractions of EUS occur during detrusor contraction, leading to detrusor-sphincter dyssynergia [20]. The damage by DM to the functional, morphological and neurotransmitter system in the urethra is the underlying cause of this dysfunction [20]. Patients with BPH and DM carry an extra EUS damage risk in terms of BPH surgery and DM itself [9, 11]. In the present study, we successfully demonstrate that HoLEP is safe and

Table 3. *Baseline and postoperative 1st and 6th month follow-up data and the patients' continence status*

	Parameters						
	PSA	IPSS-Total	Qmax (ml/s)	Qave (ml/s)	PVR	SUI (n %)	UUI (n %)
Preoperative							
Group 1	5.38 ±4.89	29 ±3.53	8 ±4.96	4 ±2.12	158 ±138.29		
Group 2	5.2 ±3.75	30 ±3.46	9 ±4.42	4.2 ±1.68	149.5 ±140.68		
p-value	0.14	0.33	0.13	0.08	0.64		
Postoperative 1st month							
Group 1	1.1 ±1.21[a]	3 ± 1.22[a]	29 ±8.38[a]	14.2 ±4.31[a]	0 ±27.08[a]	2 (1.7%)	2 (1.7%)
Group 2	1.15 ±1.32[a]	3 ±1.94[a]	28.45 ±9.42[a]	13 ±4.24[a]	10 ±20.43[a]	2 (2.1%)	2 (2.1%)
p-value	0.86	0.27	0.4	0.05	0.97	1	1
Postoperative 6th month							
Group 1	0.8 ±0.73[a]	3 ±0.87[a]	31 ±7.7[a]	15 ±4.3[a]	0 ±18.74[a]	1 (0.8%)	0 (0%)
Group 2	0.88 ±0.86[a]	3 ±1.56[a]	30.25 ±8.42[a]	14 ±4.09[a]	0 ±14.24[a]	1 (1%)	0 (0%)
p-value	0.93	0.64	0.28	0.08	0.88	1	NA

N – number of patients; PSA – prostate-specific antigen; IPSS – International Prostate Symptom Score; QoL – quality of life; PVR – post voiding residual volume; Qmax – maximum flow rate; Qave – average flow rate; SUI – stress urinary incontinence; UUI – urge urinary incontinence
[a] p <0.001 compared to baseline

Table 4. *Intraoperative and postoperative complications according to the modified Clavien–Dindo classification*

	Group 1	Group 2	p	Management
Intraoperative complications				
Haematuria requiring prolonged irrigation	3	1	0.62	Irrigation (G3a)
Capsular perforation	1	1	1	Longer catheterization, 3 days (G1)
Superficial bladder mucosal injury	1	0	1	Longer catheterization, 3 days (G1)
Device problem	0	0	NA	
Postoperative complications				
UTI	1	1	1	Intravenous antibiotic (G2)
Clot	1	1	1	Evacuation via urethral catheter-irrigation (G3a)
Clot	1	0	1	Cytoscopic evacuation
Re-catheterisation	0	0	NA	
Bladder neck contracture	0	1	1	Bladder neck laser incision (G3b)
Urethral stricture	1	0	1	Internal urethrotomy(G3b)
Meatal stenosis	0	1	1	Meatoplasty(G3b)

NA – not applicable; UTI – urinary tract infection
Statistically analysed with Pearson Chi-Square test

effective minimally invasive surgery in BPH patients with DM.

Diabetes mellitus primarily affects bladder sensations, affecting the detrusor function [21]. Kebapci et al. reported that the duration of diabetes is associated with severe bladder dysfunction, and SUI occurs in 22% of diabetic men [22]. Elmansy et al. reported that a prostate volume larger than 81 g, operation time longer than 96 minutes, PSA reduction 84% or more, and the presence of DM were significantly associated with postoperative SUI development [9]. Similarly, Houssin et al. reported that DM

is the main predictive factor of SUI, which can also be detected in the 6th month after HoLEP [9, 14]. In our study, SUI in the 6th month follow-up after HoLEP surgery was observed in one patient (1.04%) among our patients with DM; there was no significant difference between patients with and without DM here in terms of SUI (p >0.05).

Although the most common reason for SUI in men is a radical prostatectomy, approximately 10% of male SUI cases occur after benign prostate enlargement (BPE) surgery [23]. The surgical technique applied can affect postoperative incontinence. In particular,

there are various HoLEP techniques known to improve continence status by preserving EUS, one of the main factors of continence [8]. Endo et al. reported that anterior-posterior dissection via three-lobe technique reduces/limits EUS damage [24]. This technique mimics open prostatectomy, and helped reduce the postoperative SUI rate from 25.2% to 2.7% [24]. Another modified version of the three-lobe technique was described by Gong et al. and their postoperative SUI ratio was 2% [25]. We developed a novel surgical technique named the Omega sign according to the anatomical landmarks and topographic anatomy of EUS [16]. In this technique, the incisions made between the 11–1 o'clock positions preserve the sphincter structure and prevent premature sphincter relaxation and voiding problems, particularly in the early postoperative period [16]. Because EUS is a structure adjacent to the prostate capsule with a large surface between 11 to 1 o'clock location in prostate's anterior part [26, 27], this technique reduces EUS damage by protecting the anterior region. The Omega sign technique's most important step forming the mucosal flap is making mucosal incisions in which the Omega-shaped EUS and proximal part of the prostate's apex are separated immediately before enucleation. This prevents the stretching and damaging effects of blunt dissection. With this technique, SUI was significantly alleviated in the early postoperative period compared to classical three-lobe technique outcomes [16, 27].

Surgical experience can affect postoperative UI development [12, 13, 14, 28]. Longer operation times, improper enucleation and mechanical and/or thermal trauma to the EUS can cause UI [11]. During the surgeon's learning curve, prolonged surgical duration and mechanical trauma disrupt the contractility of EUS [14]. In a multicenter study, the surgical experience of at least 40 cases proved to be the main predictor for UI in the 3rd postoperative month [14]. Another multicenter study involving 1113 patients revealed that after gaining 20 years of HoLEP experience, surgery time and enucleation efficacy were associated with low UI rates in the 3rd and 6th months postoperatively [13]. Shah et al. reported that the surgeon's experience is a significant factor regarding incontinence after HoLEP [28]. The low postoperative UI rates in our study can be attributed to the surgeon's experience (LT).

Longer operation times and intraoperative bleeding can affect postoperative continence. Kobayashi et al. found that an enucleation time >100 min. and increased hemoglobin loss >2.5 g/dL were independent and significant predictors for postoperative UI [29]. Poor intraoperative visibility due to bleeding and the inappropriate operation of the laser source or resectoscope may increase the damage risk to the EUS [29]. Manipulating the resectoscope for too long can also cause transient hypotonia in the EUS complex [30]. In our study, mean TOT was under 100 min and the mean loss of Hb was under 1 g/dL in each group. There was no significant group difference in mean TOT and hemoglobin loss.

Our study has some limitations. Firstly, it is retrospective. Secondly, the patients' continence status was evaluated only at their postoperative visits, and we did not quantify the UI. Instead, we relied on the ICS definition of UI, accepting any leak as UI. In addition, we did not assess the patients' dysuria complaints – which are frequent and temporary problems for patients after HoLEP. Thirdly, we were unable to determine how long our patients had DM, due to the lack of data. Lastly, the follow-up duration was short.

CONCLUSIONS

As its complication and urinary incontinence rates are low, patients with diabetes mellitus (DM) can safely undergo Holmium laser enucleation of the prostate (HoLEP). The ideal surgical technique and surgeon's experience play an extremely important role in the success of HoLEP in patients with DM.

AUTHOR CONTRIBUTIONS

OA: project development and manuscript writing; MY: data collection and manuscript writing; HCA: statatistical analysis; SYilmaz: data collection and manuscript writing; EG: data analysis and manuscript writing; SYalcin: data collection; MD: data collection; EK: data collection and manuscript writing; AM: manuscript reviewing and editing; LT: supervision and management.

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