

# Diabetes mellitus lowers the chance of short-term urinary continence recovery in prostate cancer patients undergoing radical prostatectomy

Alexander Philippi<sup>1</sup>, Philipp Mandel<sup>1</sup>, Jan L. Hohenhorst<sup>2,3</sup>, Mike Wenzel<sup>1</sup>, Clara Humke<sup>1</sup>, Clarissa Wittler<sup>1</sup>, Jens Köllermann<sup>4</sup>, Thomas Steuber<sup>3</sup>, Markus Graefen<sup>3</sup>, Derya Tilki<sup>3,5,6</sup>, Pierre I. Karakiewicz<sup>2</sup>, Felix Preisser<sup>1</sup>, Andreas Becker<sup>1</sup>, Luis A. Kluth<sup>1</sup>, Felix K.H. Chun<sup>1</sup>, Benedikt Hoeh<sup>1,2</sup>

<sup>1</sup>Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

<sup>2</sup>Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montréal Health Center, Montréal, Québec, Canada

<sup>3</sup>Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Germany

<sup>4</sup>Dr. Senckenberg Institute of Pathology, University Hospital Frankfurt, Frankfurt am Main, Germany

<sup>5</sup>Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

<sup>6</sup>Department of Urology, Koc University Hospital, Istanbul, Turkey

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## Corresponding author

Benedikt Hoeh  
University Hospital Frankfurt  
Department of Urology  
7 Theodor-Stern-Kai  
60590 Frankfurt am Main,  
Germany  
phone: +49 69 6301 83147  
benedikt.hoeh@kgu.de

**Introduction** The aim of this article was to test the impact of diabetes mellitus (DM) on short-term urinary continence in patients undergoing radical prostatectomy (RP).

**Material and methods** We relied on an institutional tertiary-care database to identify patients who underwent RP between 11/2018 and 02/2021 with data available on short-term urinary continence status (30–90 days post-surgery). Continence was defined as the usage of no or one safety-pad within 24 hours. Univariable and multivariable logistic regression models tested the correlation between DM and short-term continence. Covariates consisted of pathological T-stage, body mass index, prostate volume, surgical approach and nerve-sparing.

**Results** Of 142 eligible patients, 15 (11%) patients exhibited concomitant DM. Patients diagnosed with DM exhibited lower continence rates at short-term follow-up compared to patients without DM (33 vs 63%,  $p = 0.03$ ). In univariable and multivariable logistic regression models, DM was strongly associated with reduced chances of short-term urinary continence recovery (multivariable odds ratio [OR]: 0.26, 95%-CI: 0.07–0.86;  $p = 0.03$ ). Furthermore, pathological T-stage (pT3/pT4) was additionally associated with reduced chance of urinary continence in logistic regression models (multivariable OR: 0.43, 95%-CI: 0.19–0.94;  $p = 0.04$ ). Other covariables failed to reach statistical significance in multivariable logistic regression analyses predicting urinary continence.

**Conclusions** DM was associated with lower chances of short-term urinary continence recovery in a contemporary cohort of patients undergoing radical prostatectomy. Patients with DM should be preoperatively informed and intensified, postoperative pelvic floor training should be considered in this subgroup of RP patients.

**Key Words:** diabetes mellitus ↔ radical prostatectomy ↔ short-term urinary continence ↔ functional outcomes ↔ prostate cancer

## INTRODUCTION

Urinary incontinence after radical prostatectomy (RP) remains a bothersome complication for pros-

tate cancer (PCa) patients and is frequently associated with a substantial loss of quality of life in affected patients [1–5]. In the past, extensive research has been conducted to identify preoperative factors

which are likely to affect postoperative urinary continence, such as body mass index (BMI), age or prostate volume [6–10]. Surprisingly however, studies investigating the effect of concomitant diabetes mellitus (DM) on functional outcomes in PCa patients treated with RP are scarce. Huang et al. recently reported in a systematic review, relying on only seven eligible studies investigating the role of DM that concomitant DM was only associated with an adverse impact on the recovery of urinary continence at intermediate follow-up (defined as follow-up at 12 month) period [11–18]. It is of note that five of these seven studies relied on patients undergoing RP before 2014. Subsequently, these findings may not be transferable to more contemporary study cohorts, since surgical techniques have substantially evolved in the meantime [19–21]. Moreover, among the three studies specifically investigating the effect of DM on short-term urinary continence, results were inconclusive [13, 17, 18]. In regards to the known negative effects of DM on wound healing, as well as diabetic microcirculation disorder and neuropathy, we hypothesized that concomitant DM is associated with lower chances of short-term urinary continence recovery [22–26]. To address this uncertainty, we relied on a most contemporary cohort of PCa patients (2018 to 2021) treated with RP.

## MATERIAL AND METHODS

### Study population

From 11/2018 to 02/2021, 565 patients treated with RP were retrospectively identified from our prospective institutional database. Of those, 142 patients (25.1%) were subsequently identified with data available for short-term urinary continence status (30–90 days post-surgery). Indication for RP was histologically confirmed prostate cancer. All surgeons, who performed RP in the current cohort, were experienced surgeons trained in high-volume prostate cancer centers. RP was routinely performed with full functional-length urethral sphincter (FFLU) and neurovascular bundle preservation (NVBP) with intraoperative frozen section technique (IFT), as previously described [2, 20].

### Outcome measurements

Short-term urinary continence was defined as the use of no or one safety pad within 24 hours, whereas a higher number of pads was considered incontinent. More precisely, data regarding daily pad usage was assessed by evaluating the number of pads used, grouped as '0 – one safety', '1–2', '3–5' or '>5'

pads, respectively [27]. Data on urinary continence status was extracted of voluntary self-reported standardized, validated questionnaires, as previously described [1, 27].

### Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. The chi-square test examined the statistical significance of the differences in proportions while the Kruskal-Wallis test was used to examine differences in medians.

Statistical analyses consisted of three steps. First, patients and tumor characteristics were tabulated according to DM status. Second, rates of short-term urinary continence were calculated in the overall cohort. Subsequently, urinary continence rates were separately recalculated, after stratification to DM. Third, univariable and multivariable logistic regression models tested the relationship between DM and short-term urinary continence (0–1 vs  $\leq 1$  pads/24 hours). Covariates consisted of organ confined/non-organ confined stage (pT2 vs pT3/4), BMI (continuously coded), age (continuously coded), prostate volume (continuously coded), surgical approach (open RP vs robotic-assisted RP) and nerve-sparing approach (no vs yes). Moreover, univariable and multivariable logistic regression models were repeated with age ( $\leq 60$  vs 61–69 vs  $\geq 70$  years), BMI ( $< 25$  vs 25–30 vs  $\geq 30$  kg/m<sup>2</sup>) and prostate volume ( $\leq 40$  vs  $> 40$  ml) as categorical variables.

To test for a potential underlying selection bias, sensitivity analyses were performed between the current study cohort and patients with missing data regarding short-term urinary continence (11/2018 to 02/2021).

For all statistical analyses R software environment for statistical computing and graphics (version 3.4.3) was used [28]. All tests were two-sided with a level of significance set at  $p < 0.05$ .

## RESULTS

### Descriptive characteristics of the study population

In total, 142 patients were included in the current analysis (Table 1). Of those, 15 patients (11%) exhibited DM at time of RP. The majority of patients underwent robotic-assisted RP (77% in the overall cohort). Patients with DM exhibited statistically significant higher median BMI rates (28.6, IQR: 27.7–31.0 vs 26.5 IQR: 24.5–29.0;  $p = 0.005$ ). Besides BMI, no statistically significant differences were recorded for patients and tumor characteristics be-

**Table 1.** Patient and clinicopathological characteristics of 142 patients treated with radical prostatectomy between 11/2018 and 02/2021 with data available for short-term continence (30–90 days post-surgery), stratified by diabetes mellitus status. All values are Median (IQR) or frequencies (%)

	Overall (n = 142)	No diabetes mellitus (n = 127)	Diabetes mellitus (n = 15)	P-value
Age in years, Median (IQR)	66 (60, 71)	65 (60, 70)	70 (62, 72)	0.3
Age grouped in years, n (%)				0.2
≤60	37 (26%)	34 (27%)	3 (20%)	
61–69	60 (42%)	56 (44%)	4 (27%)	
≥70	45 (32%)	37 (29%)	8 (53%)	
PSA in ng/ml, Median (IQR)	8 (6, 12)	8 (6, 12)	6 (6, 9)	0.2
Body mass index in kg/m <sup>2</sup> , Median (IQR)	26.6 (24.6, 29.3)	26.5 (24.5, 29.0)	28.6 (27.7, 31.0)	0.005
Body mass index grouped in kg/m <sup>2</sup> , n (%)				0.048
≤25	42 (30%)	41 (32%)	1 (6.7%)	
25–30	70 (49%)	62 (49%)	8 (53%)	
≥30	30 (21%)	24 (19%)	6 (40%)	
D'Amico risk classification, n (%)				0.5
low	14 (10%)	12 (10%)	2 (13%)	
intermediate	84 (60%)	77 (61%)	7 (47%)	
high	43 (30%)	37 (29%)	6 (40%)	
Operation time in min, Median (IQR)	216 (185, 253)	215 (184, 250)	238 (203, 260)	0.2
Prostate volume in ml, Median (IQR)	40 (31, 60)	40 (30, 58)	49 (36, 59)	0.4
Nerve-sparing approach, n (%)	132 (93%)	118 (93%)	14 (93%)	>0.9
Positive surgical margin, n (%)				0.9
RO	95 (67%)	84 (66%)	11 (73%)	
R1	43 (30%)	39 (31%)	4 (27%)	
RX	4 (2.8%)	4 (3.1%)	0 (0%)	
Surgical approach, n (%)				0.10
robotic-assisted RP	110 (77%)	101 (80%)	9 (60%)	
open RP	32 (23%)	26 (20%)	6 (40%)	
Gleason grade group, n (%)				0.9
1	25 (18%)	23 (19%)	2 (14%)	
2	66 (48%)	59 (48%)	7 (50%)	
3	27 (20%)	23 (19%)	4 (29%)	
4	5 (3.6%)	5 (4.1%)	0 (0%)	
5	14 (10%)	13 (11%)	1 (7.1%)	
n.a.	5 (3.6%)	4 (3.1%)	1 (7.1%)	
pT-stage combined, n (%)				0.4
pT2	81 (57%)	71 (56%)	10 (67%)	
pT3/T4	61 (43%)	56 (44%)	5 (33%)	
pN-stage, n (%)				0.3
pN0	116 (82%)	104 (82%)	12 (80%)	
pN1	10 (7.0%)	10 (7.9%)	0 (0%)	
pNx	16 (11%)	13 (10%)	3 (20%)	

PSA – prostate-specific antigen; RP – radical prostatectomy; IQR – interquartile range; RP – radical prostatectomy

tween patients with and without DM (Table 1). The majority of patients was diagnosed with DM type 2 (87%). Among those, biguanide/gliptin-combination (38%), monotherapy of biguanide (30%), as well as insulin therapy (15%) were the most frequent treatment schemes.

### Short-term urinary continence outcomes

Median-follow up time for short-term urinary outcomes was 69 (IQR: 61–77) vs 59 (IQR: 43–74) days for patients with vs patients without DM, respectively ( $p = 0.07$ ). Overall rate of short-term urinary continence was 60% (Table 2). Patients with concomitant DM exhibited statistically significant lower rates of urinary continence compared to patients without DM (63 vs 63%,  $p = 0.03$ ). Rates of usage of 1–2, 3–5, >5 pads were 40%, 27%, 0% and 19%, 16%, 2.4% for patients with DM and patients without DM, respectively (Table 2;  $p = 0.09$ ).

### Univariable and multivariable logistic regression models

In univariable logistic regression models, DM was a statistically significant factor influencing short-term urinary continence and resulted in a univariable OR of 0.29 (95%-CI: 0.09–0.88;  $p = 0.03$ ) (Table 3). After adjustment for other covariates, DM remained a statistically significant factor influencing short-term urinary continence in multivariable logistic regression models (OR: 0.26, 95%-CI: 0.07–0.86;  $p = 0.03$ ). Moreover, in univariable and multivariable logistic regression models, presence of non-organ

**Table 2.** Short-term continence rates (30–90 days post-surgery) of 142 patients treated with radical prostatectomy between 11/2018 and 02/2021, stratified according to diabetes mellitus status. All values are median (IQR) or frequencies (%)

	Overall (n = 142)	No Diabetes mellitus (n = 127)	Diabetes mellitus (n = 15)	p-value
Follow-up time in days, Median (IQR)	60 (44, 76)	59 (43, 74)	69 (61, 77)	0.07
Short-term continence, n (%)				0.03
No	57 (40%)	47 (37%)	10 (67%)	
Yes	85 (60%)	80 (63%)	5 (33%)	
Numbers of pads/24h, n (%)				0.09
0–1 (safety pad)	85 (60%)	80 (63%)	5 (33%)	
1–2	30 (21%)	24 (19%)	6 (40%)	
3–5	24 (17%)	20 (16%)	4 (27%)	
>5	3 (2.1%)	3 (2.4%)	0 (0%)	

IQR – interquartile range

**Table 3.** Uni- and multivariable logistic regression models predicting short-term (30–90 days post-surgery) urinary continence in 142 patients treated with radical prostatectomy. Urinary continence was defined by usage of no or one safety pad within 24h

	Univariable				Multivariable			
	Odds ratio	95%-CI		P-value	Odds ratio	95%-CI		P-value
		2.5%	97.5%			2.5%	97.5%	
Diabetes mellitus								
No	Ref.				Ref.			
Yes	0.29	0.09	0.88	0.03	0.26	0.07	0.86	0.03
pT-stage combined								
pT2	Ref.				Ref.			
pT3/4	0.40	0.20	0.80	0.01	0.43	0.19	0.94	0.04
Body mass index in kg/m <sup>2</sup>	0.98	0.89	1.08	0.73	1.03	0.93	1.15	0.56
Age in years	0.98	0.94	1.03	0.45	0.98	0.93	1.04	0.56
Prostate volume in ml	1.01	0.99	1.03	0.21	1.01	1.00	1.03	0.12
Surgical approach								
open RP	Ref.				Ref.			
robotic-assisted RP	2.77	1.25	6.33	0.01	2.35	0.92	6.18	0.08
Nerve-sparing approach								
No	Ref.				Ref.			
Yes	3.83	1.01	18.38	0.06	1.57	0.32	8.93	0.58

RP – radical prostatectomy; 95%-CI – 95%-confidence-interval

confined (defined as presence of pT3 or pT4 at final RP-specimen) was a statistically significant factor influencing short-term urinary continence (multivariable OR: 0.43; 95%-CI: 0.19–0.94;  $p = 0.04$ ). Results of univariable and multivariable logistic regressions remained qualitatively unchanged, when analyses were repeated with age, BMI and prostate volume as categorical variables. All other variables had an insignificant influence on early urinary continence in multivariable analyses (Table 3).

### Sample selection bias

Sensitivity analyses was performed for potential selection bias due to differences in tumor and patient characteristics between the study cohort ( $n = 142$ ) and patients with missing data regarding early continence rates in the study period ( $n = 423$ ). Here, no significant differences between the current study cohort and the entire cohort were recorded (all  $p \geq 0.1$ ).

## DISCUSSION

At present DM is one of the most frequent disease among elderly patients and prevalence of DM type 2 has rapidly increased in last decades in most industrialized countries due to lifestyle changes [29]. Both diabetic microangiopathy and diabetic neuropathy are known side-effects of DM, which are associated with prolonged, restrictive wound healing process [25, 26, 30]. As a consequence, we hypothesized that concomitant DM was associated with lower chances of short-term urinary continence recovery in PCa pa-

tients undergoing RP. We relied on a contemporary cohort of PCa patients (2018 to 2021) undergoing RP at a tertiary referral center and made some noteworthy findings.

First, patients diagnosed with DM exhibited lower rates of urinary continence in short-term follow-up compared to patients without DM. With a continence rate of only 33%, two out of three DM patients were incontinent in short-term follow-up. Conversely in the absence of DM, the majority of patients (63%) reported urinary continence at short-term follow-up ( $p = 0.03$ ). Undergoing surgical treatment, irrespectively of the type and magnitude of the intervention, is inevitably associated with iatrogenic damage to the surrounding tissue in the operating field. In PCa patients undergoing RP, postsurgical urinary continence is predominantly dependent on an recovered sphincteric system, which is non-negotiable exposed to stress and tissue damage during RP [13, 31, 32]. Since DM is strongly associated with conditions that attenuate tissue repair and healing process, such as microvascular circulation disorder or neuropathy, it is very likely that differences in short-term urinary continence rates are attributable to a delayed recovery and healing process in DM patients [30]. Additionally, it is plausible that the sphincteric system of DM patients is already pre-operative exposed to microcirculation disorders and to diabetic neuropathy, which furthermore might attribute to lower rates of urinary continence at short-term follow up. In line with our findings, Teber et al. reported similar findings in regards to short-term urinary continence. Urinary continence

rates of DM patients undergoing RP were significantly lower compared to patients without concomitant DM (43.7% vs 57.8%;  $p = 0.03$ ) [13]. Differences and limitations between the study by Teber et al. and the current study occur due to the historical study cohort (1999–2008) of Teber et al. [13].

Second, in univariable logistic regression models, DM was strongly associated with lower chances of short-term urinary continence in the current study population. Interpretation of these findings without accounting for other potential influencing factors can result in a deterred conclusion, overestimating the effect of DM on short-term urinary continence. As a consequence, in order to specifically investigate the effect of DM on short-term urinary continence, we additionally relied on multivariable logistic regression models to adjust for this potential bias. Interestingly, the meaningful predictor status of DM remained qualitatively and quantitatively unchanged after adjustment for other potential variables. Since DM remained statistically significant even after adjustment for other covariables, results indicate that DM itself is associated with lower chances of urinary continence recovery at short-term follow-up [6]. Contrary to the current findings, DM failed to reach statistical significance status in a study reported by Mao et al., who investigated the magnitude of preoperative risk factors on urinary continence in PCa patients undergoing RP [15]. Since nerve-sparing performance was a primary exclusion criterion in the study design by Mao et al., results cannot be directly compared to the current study, since the vast majority of patients in the current study received nerve sparing (93%) [15]. In contrast to the findings by Mao et al., yet in agreement with our findings, Cakmak et al. as well as Teber et al. reported a statistically significant association of DM with urinary continence rates at different follow-up periods [13, 15, 17].

Third, even though not being the primary focus of the current study, extracapsular extension of the tumor (defined as pT3/pT4) was independently associated with lower chances of short-term urinary continence (Table 3). These findings are in line with previous reports and can be explained by the necessity of a more extensive broader resection due to the non-organ confined disease of the tumor.

Despite these noteworthy findings, the current study is not devoid of limitations. First, limitations inherent to the retrospective nature of the study and the limited sample size have to be addressed. Second, a potential bias regarding the extent of postsurgical pelvic-floor training cannot be ruled out. However, all patients were strongly encouraged to seek professional pelvic-floor training and were already instructed during their in-patient stay. Third, differences

in experience among the surgeons might have been present [33]. However, it is of note that all surgeons underwent training in high-volume prostate cancer centers and procedures were performed according to a standardized protocol. Fourth, the current effect of DM on urinary continence may differ from the one on long-term continence rates. Here, not only follow-up timepoints of 12 months but also extended time spans (24 months) would be of great interest. Previously, different authors have reported remarkable improvement in long-term continence rates beyond 12 months of follow-up [5, 10, 34]. Unfortunately, despite the very important findings of those studies, none of the studies investigated the role of DM on long-term continence outcomes. Fourth, time span between DM diagnosis and RP is not available in the current study. As a consequence, no further comments can be made in regard to a time depending effect of DM and short-term urinary continence status. Besides the very important primary endpoint of urinary continence, upcoming studies should investigate the role of DM on other, equally important functional outcomes, which may contribute to the overall quality of life in RP treated patients [5]. Finally, all limitations that are inherently linked to data derived from voluntary, self-questionnaire reporting, such as potential selection bias, should be taken into consideration while interpreting the current study.

## CONCLUSIONS

DM was associated with lower chances of short-term urinary continence recovery in a contemporary cohort of patients undergoing radical prostatectomy. Patients with DM should be preoperatively informed and can help with patient counseling by offering a more personalized and more accurate prediction of expected, postsurgical results.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ETHICS CONSENT STATEMENT

The study was approved by the institutional review boards of the University Cancer Centre Frankfurt and the Ethical Committee at the University Hospital Frankfurt. All patients included in our study signed a written informed consent.

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## AUTHOR CONTRIBUTIONS

Alexander Philippi: conceptualization; data acquisition, formal analysis; original draft preparation

Philipp Mandel: conceptualization; formal analysis; supervision  
 Mike Wenzel: data acquisition; formal analysis and investigation  
 Clara Humke: conceptualization; data acquisition  
 Felix Preisser: conceptualization; data acquisition  
 Clarissa Wittler: conceptualization; data acquisition  
 Jan L. Hohenhorst: writing and editing  
 Jens Köllermann: data acquisition  
 Thomas Steuber: conceptualization  
 Markus Graefen: writing – reviewing and editing

Derya Tilki: conceptualization; writing – reviewing and editing  
 Pierre I. Karakiewicz: conceptualization; writing – reviewing and editing  
 Andreas Becker: conceptualization; writing – reviewing and editing  
 Luis A. Kluth: conceptualization; original draft preparation  
 Felix K.H. Chun: conceptualization; writing – reviewing and editing; supervision  
 Benedikt Hoeh: conceptualization; formal analysis; supervision; formal analysis

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