Urodynamics in Early Diagnosis of Diabetic Bladder Dysfunction in Women: A Systematic Review and Meta-Analysis

Background: Urodynamics can detect subtle voiding changes before cystopathy symptoms manifest. The aim of the present study was to assess urodynamic changes in diabetic women.

Material/Methods: A systematic search was performed on 04 November 2021 to identify studies reporting urodynamic parameters in diabetic women. Data were analyzed in a single-arm meta-analysis due to lack of sufficient studies with direct comparisons to healthy women. For data synthesis, a random-effects model with restricted maximum-likelihood estimation was applied. The calculated effect sizes were visualized in forest plots. Statistical heterogeneity was assessed using the $I^2$ measure and the $c^2$ test. The risk of bias was assessed using the QUIPS tool. PROSPERO ID: CRD42021256275.

Results: Out of 1750 records, 10 studies were used in the analysis (n=2342 diabetic women). Pooled event rates showed that mean voided volume was 288.21 mL [95% confidence interval (CI): 217.35-359.06, $I^2=98%$], mean post-void residual volume was 93.67 mL [95% CI: 31.35-155.99, $I^2=100%$], mean $Q_{\text{max}}$ was 18.80 mL/sec [95% CI: 15.27-22.33, $I^2=99%$], mean $P_{\text{det}}Q_{\text{max}}$ is 30.13 cmH$_{2}$O [95% CI: 25.53-34.73, $I^2=90%$], mean first sensation of bladder filling was 178.66 mL [95% CI: 150.59-206.72, $I^2=97%$], and mean cystometric capacity was 480.41 mL [95% CI: 409.32-551.50, $I^2=98%$] in diabetic women.

Conclusions: Pooled results indicate that diabetic women tend to have a smaller voided volume, slower $Q_{\text{max}}$ and $P_{\text{det}}Q_{\text{max}}$, larger postvoid residual, and higher first sensation of bladder filling and cystometric capacity compared to the general female population.

Keywords: Diabetes Complications • Diabetes Mellitus • Diabetic Neuropathies • Meta-Analysis • Systematic Review • Urodynamics • Urology

Abbreviations: BMI – body mass index; BOO – bladder outlet obstruction; CENTRAL – Cochrane Central Register of Controlled Trials; CI – confidence interval; DC – diabetic cystopathy; $k$ – Cohen's kappa; LUTS – lower urinary tract symptoms; MCC – maximum cystometric capacity; mL – milliliter; OAB – overactive bladder; $P_{\text{det}}Q_{\text{max}}$ – maximal detrusor pressure at maximal flow rate; PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses; $Q_{\text{ave}}$ – average flow rate; $Q_{\text{max}}$ – maximum flow rate; $Q_{\text{acc}}$ – urine flow acceleration ($Q_{\text{max}}/TQ_{\text{max}}$); QUIPS – Quality in Prognostic Studies; REML – restricted maximum likelihood; $TQ_{\text{max}}$ – time to maximum flow rate; UB – underactive bladder

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/937166
Background

Diabetic cystopathy (DC) is a well-recognized urological complication of diabetic autonomic neuropathy [1]. The classic triad of DC is decreased bladder sensation, increased bladder capacity, and impaired bladder emptying with postvoid residual volume [2-6]. Patients usually have overactive bladder or overflow incontinence, including urinary frequency, urgency, incontinence, and nocturia, which are listed among the lower urinary tract symptoms (LUTS) [7,8].

DC gradually progresses over time from an initial compensated [typically manifests as overactive bladder (OAB)] to a later decompensated [typically manifests as underactive bladder (UB)] phase that cause storage or voiding LUTS [9,10].

Uroflowmetry is a simple urodynamic diagnostic tool to measure voided volume and maximum flow rate. Cystometry measures pressure/volume relationship of bladder during the filling (storage) phase of the micturition cycle via a catheter. As urodynamics can detect subtle voiding changes even before the manifestation of LUTS, urodynamic evaluation can be useful in the early diagnosis of DC.

The normative reference values for bladder function by urodynamics in healthy women have been described earlier [11,12], but the literature on diabetic women is scant. Therefore, our aim was to assess urodynamic alterations in diabetic women.

Material and Methods

The study is reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 Statement [13].

Study protocol

The study was in line with the protocol registered on 23 May 2021, and can be found under the registration number: CRD42021256275 in PROSPERO. A review protocol was not prepared.

Our primary aim was to compare the urodynamic parameters of diabetic women to those of healthy women, but the eligible studies according to our inclusion criteria did not provide sufficient raw data on healthy women. Since a direct comparison could not be implemented in diabetic and non-diabetic patients, we conducted a single-arm meta-analysis and positive event rates were pooled for statistical analysis. Furthermore, our intent was to detect changes in voiding in diabetic women with cystopathy compared to diabetic women without peripheral neuropathy by uroflowmetry, but the eligible studies did not contain sufficient raw data to conduct the analysis. Otherwise, we fully adhered to the study protocol.

Systematic Search

Two review authors (ÁRM and PP) independently carried out the systematic literature search in Embase, MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Web of Science. The authors applied the following keywords: (urodynamic or uroflow* or uroflowmetry) and (diabetes or diab*) (Supplementary Table 1) on 04 November 2021. In each database, they applied “All text” or “All fields” in the search bar avoiding any filters or restrictions regarding publication year, language, and place of origin. They reviewed the included studies to find any articles previously missed in the original search.

Selection and Eligibility

The authors included case-control and cohort studies, as well as full-text articles and conference abstracts in the synthesis of quantitative and qualitative data to reduce selection bias. Case reports featuring single patients were excluded. In case of potentially overlapping study populations (based on authors, sites, patients and urodynamic parameters), those with better quality of data were included.

Eligible studies had to provide data on diabetic women, with or without voiding disorder, and urodynamic parameters [14], which include uroflowmetry and cystometry parameters [15,16]. Regardless of the method of measurement (with ultrasonography or via catheter), postvoid residual volume (in mL) was also included in the analysis. Studies that included both sexes were included if they performed subgroup analysis for diabetic women.

Articles examining patients after kidney transplantation or surgery affecting the genitourinary tract, patients with neurogenic bladder dysfunction and other neurological disease (eg, progressive neurological conditions such as Parkinson’s disease, dementia, multiple sclerosis) except peripheral neuropathy; pregnant women and women within first 6 months postpartum, end-stage kidney disease, or kidney transplants were excluded, since they can influence urodynamic parameters per se, causing indistinguishable confounding factors.

The records were selected via a standard three-phased process including titles, abstracts, and full-texts independently by the 2 review authors (ÁRM and PP) with EndNote X9.1.1 software (2020 Clarivate™ Analytics, Philadelphia, PA, USA). They resolved any disagreements in any phase through consensus, and calculated the Cohen’s kappa in each phase to test inter-rater reliability.
Data extraction

The 2 independent review authors (ÁRM and PP) extracted the data into a purpose-designed data collection table, with any disagreements resolved by consensus. The following data were extracted from each study: 1) study information (first author, year of publication, recruitment period, country of origin), 2) study design and methodology (retrospective versus prospective, inclusion and exclusion criteria, single versus multicenter study), 3) patient information (number of patients, mean age, definition of diabetes, type of diabetes, diabetes duration, body mass index (BMI), HbA1c values, diabetes treatment, diabetic complication), 4) LUTS assessment and symptoms, DC and peripheral neuropathy existence, and 5) urodynamic parameters of diabetic patients (voided volume, postvoid residual, $Q_{\text{max}}$, $P_{\text{det}}$, and volume at first sensation, maximal cystometry capacity).

Statistical analysis

Cohen’s kappa ($\kappa$) was calculated to test interrater reliability. It ranges from -1 to +1, where values ≤0 indicates no agreement (which are unlikely in practice), 0 represents the amount of agreement that can be expected from random chance, and 1 represents perfect agreement between the review authors. $\kappa$ results should be interpreted as the followings: values ≤0 as indicating “no agreement”, 0.01-0.20 as “none to slight”, 0.21-0.40 as “fair”, 0.41-0.60 as “moderate,” 0.61-0.80 as “substantial”, and 0.81-1.00 as “almost perfect” agreement [17].

For data synthesis we used the random-effects model with restricted maximum-likelihood (REML) estimation in all cases; means and 95% confidence intervals (CIs) were calculated. The calculated effect sizes were visualized in forest plots. Heterogeneity was tested using Cochrane’s $Q$ and the $I^2$ statistics. $I^2$ statistic represents the percentage of the total variability across studies: 30% to 60%, 50% to 90%, and 75% to 100% corresponded to “moderate”, “substantial”, and “considerable” degrees of heterogeneity, respectively, based on the Cochrane’s handbook for Systematic Reviews of Interventions [18]. We considered the Q test significant if $P<0.1$. Statistical analyses were carried out using R statistical software (version 4.0.5) and package meta (version 4.18-1). We created a single-arm meta-analysis based on urodynamic parameters and the results are graphically presented in forest plots.
Risk of bias assessment

The risk of bias of the studies were evaluated by 2 independent review authors (ÁRM and PP) using the Quality In Prognostic Studies (QUIPS) tool [19]. The result of the assessment was graphically demonstrated; any disagreements were resolved by consensus among the review authors.

To judge overall risk, the review authors (ÁRM and PP) described studies with a low risk of bias as those in which at least 5 of the 6 important bias domains (study participants, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis) were rated as having low risk of bias. If there was at least 1 domain rated as high risk, or more than 3 domains rated as moderate risk of bias, the overall risk of bias was deemed high. All other variations were determined as moderate risk of bias.

When the study design could not be identified, study attrition was not evaluated and was thus labeled as ‘grey’. Grey means not applicable or not reported.

There were not enough studies in the analyses to evaluate publication bias by funnel plots and statistical tests.

Table 1. Baseline characteristics of the included studies.

| First author          | Country (centers) and recruitment period | Study design         | Inclusion criteria                                                                 |
|-----------------------|------------------------------------------|----------------------|------------------------------------------------------------------------------------|
| Al Timimi et al 2020  | Iraq (single) 2018-2019                   | Prospective cross-sectional | Patients with T2DM at least 5 years with LUTS                                        |
| Changxiao et al 2014  | China (multi) 2010-2013                   | Prospective cross-sectional | Women aged ≥18 years with DM                                                       |
| Galí et al 2015       | Italy (single) 2008-2010                  | NA                   | Patients with T2DM at least 5 years with moderate/severe LUTS                       |
| Golabek et al 2012    | Republic of Ireland (single) 2004-2008   | Retrospective cohort  | Diabetic female with OAB, defined as an involuntary rise in detrusor pressure of greater than 5 cm H2O during filling |
| Lee et al 2007        | Taiwan (single) 2002-2003                 | NA                   | Women with T2DM with no concurrent neurologic disorder or medical conditions that could interfere with voiding function, without bladder dysfunction |
| Løwenstein et al 2021 | Denmark (multi) 2016-2020                | Prospective randomized | Adult women with symptoms of urinary incontinence, urgency and nocturia             |
| Malik et al 2020      | USA (multi) 2010-2014                    | Prospective          | Female patients with urology-based voiding dysfunction and no neurologic disease    |
| Shin et al 2016       | South Korea (single) 2008-2015           | Retrospective cohort  | Women without BOO who were diagnosed with SUI                                       |
| Tai et al 2009        | Taiwan (single) 2005-2007                 | Prospective          | Women with T2DM, age 50-75 years                                                    |
| Yenilmez et al 2008   | Turkey (single) 2004-2007                 | Prospective cross-sectional | Patients with T2DM and LUTS                                                          |

Results

Study Selection

Out of 1750 records (MEDLINE, n=454; EMBASE, n=773; CENTRAL, n=63; and Web of Science, n=460), a total of 140 articles were assessed for eligibility by full text, of which 10 studies [20-29] were used in the quantitative synthesis. x of the title selection was 0.99 (99.7% agreement), 0.98 (99.3% agreement) of the abstract selection, and 0.99 (99.8% agreement) of the full-text selection. The flowchart and reasons for exclusions on full-text assessment is illustrated in Figure 1.

Study Characteristics

The baseline characteristics of the included studies are reported in Table 1. Studies took place in 9 different countries, and were published between 2002 and 2020. Six studies were prospective [20,21,25,26,28,29], 2 were retrospective cohorts [23,27], and 2 studies did not provide sufficient information about study design [22,24].
| First Author | LUTS assessment | No. of patients with LUTS (%) | No. of patients with urge incontinence (%) | No. of patients with stress incontinence (%) | No. of patients with OAB (%) | No. of patients with peripheral neuropathy (%) |
|--------------|-----------------|------------------------------|------------------------------------------|------------------------------------------|----------------------------|---------------------------------------------|
| Al Timimi et al 2020 [20] | NA | 71 (100%) | 3 (4.2%) | 3 (4.2%) | 13 (18.3%) | 31 (43.7%) | NA |
| Changsiao et al 2014 [21] | IUA/ICS | 1525 (93%) | NA | NA | 918 (55.9%) | 1558 (95%) | NA |
| Gai et al 2015 [22] | IPSS, QoL, OAB-q, ICI-SF | 19 (100%) | 14 (73.7%) | 4 (21%) | 15 (79%) | NA | 14 (73.7%) |
| Golabek et al 2012 [23] | NA | 29 (100%) | 15 (51%) | 0 | 29 (100%) | 29 (100%) | NA |
| Lee et al 2007 [24] | AUA-SI | 47 (100%) | NA | NA | 0 | 47 (100%) | 18 (38.3%) |
| Lewenstein et al 2021 [25] | ICIQ-UI SF, ICIQ-OAB | 31 (100%) | NA | 4 (12.9%) | 4 (12.9%) | NA | 4 (12.9%) |
| Malik et al 2020 [26] | NA | 96 (100%) | 10 (11%) | 44 (45%) | 21 (24%) | NA | NA |
| Shin et al 2016 [27] | NA | 92 (100%) | 0 | 92 (100%) | 0 | NA | NA |
| Tai et al 2009 [28] | AUA-SI IUSS | 100 (36.7%) | 49 (18%) | 30 (11%) | NA | NA | 52 (19.1%) |
| Yenilemez et al 2008 [29] | NA | 45 (100%) | NA | NA | NA | 0* | 17 (37.7%) |

Ten full-text articles were included with a total of 2342 diabetic female patients from 9 countries. The majority of the patients (2055 – 87.7%) had LUTS; 1620 diabetic patients had urodynamic measurements and thus were included in the meta-analysis.

* Diabetic cystopathy was defined as postvoid residual volume greater than 100 mL. * Diabetic cystopathy was defined as an increase in bladder capacity (more than 500 mL), impaired bladder sensation and decrease bladder contractility. AUA-SI – American Urological Association Symptom Index; DC – diabetic cystopathy; DM – diabetes mellitus; ICIQ-OAB – International Consultation of Incontinence Questionnaire – Overactive bladder questionnaire; ICIQ-UI – International Consultation of Incontinence Questionnaire Urinary Incontinence Short Form; ICI-SF – International Consultation on Incontinence – Short form; IPSS – International Prostate Symptom Score; IUA/ICS: International Urogynecological Association/International Continence Society Standardization of Terminology Reports; IUSS – Indevus Urgency Severity Scale; LUTS – lower urinary tract symptoms; NA – not available data (not reported); OAB – overactive bladder (detrusor overactivity); OAB-q – Overactive Bladder Questionnaire; QoL – Quality of life Questionnaire; SUI – stress urinary incontinence; T2DM – type 2 diabetes mellitus.

**General Characteristics of Diabetic Women**

We included 10 studies to the quantitative synthesis that reported on a total of 2342 diabetic patients, including 2055 patients (87.7%) with LUTS. The majority of the patients had type 2 diabetes. In 7 studies, the type of diabetes was reported [20-24,28,29], while in 3 studies [25-27] it was not, although they had small number of patients. The mean age of the study populations ranged between 52.75±9.2 and 64.7±11.1 years, the mean duration of diabetes ranged between 8.04±0.69 and 12.42±7.3 years, the mean BMI ranged between 22.8±2.4 and 33.2±7.8 kg/m², and the mean HgA1c ranged between 6.05±2.38 and 9.1±2.6%. The demographic characteristics of diabetic patients are presented in Table 2.

**Urodynamic Parameters of Diabetic Women**

The urodynamic parameters of the diabetic women were assessed qualitatively. These data are reported in Table 3.
### Voided Volume

The pooled event rates show that mean voided volume in diabetic women (n = 471) was 288.21 mL [95% CI: 217.35-359.06] with a considerable level of heterogeneity ($I^2$=98%) (Figure 2A).

### Postvoid Residual Volume

The pooled event rate represents that mean postvoid residual volume in diabetic women (n=1589) was 93.67 mL [95% CI: 31.35-155.99] with a considerable level of heterogeneity ($I^2$=100%) (Figure 2B).
First Sensation of Bladder Filling

The mean first sensation of bladder filling in diabetics (n=1201) was 178.66 mL [95% CI: 150.59-206.72] with a considerable level of heterogeneity ($I^2=97\%$) (Figure 2E).

Cystometric capacity

The mean maximum cystometric capacity (MCC) in diabetic women (n=1178) was 480.41 mL [95% CI: 409.32-551.50] with a considerable level of heterogeneity ($I^2= 98\%$) (Figure 2F).

Risk of bias assessment

A summary of the risk of bias assessment is visually presented in Supplementary Figure 1.

In the analysis of female diabetic patients' urodynamic parameters, the majority of the studies had a high overall risk of bias [20,22-27,29]. The main reasons include confounding factors, such as unreported 1) diabetes definition, 2) diabetes duration, 3) HgA1c, 4) diabetes treatment, 5) BMI, 6) LUTS assessment, 7) device and methodology of the uroflowmetry measurement, 8) measuring method of postvoid residual volume, and 9) statistical analysis. Existence of pyuria was a confounding factor as well. One study had moderate overall risk of bias because not all patients were included in the urodynamic analysis, and an assessed confounding factor was that BMI was not reported [21]. One study was reported as having low overall risk of bias [28].

Discussion

Summary of Evidence

Lower mean voided volume, $Q_{\text{max}}$ and $P_{\text{det}}Q_{\text{max}}$, as well as higher mean postvoid residual volume, first sensation of bladder filling, and cystometric capacity in the diabetic group was detected compared to healthy women [11,12].

### Table 3. Baseline characteristics of urodynamic parameters of diabetic women in the included studies.

| First Author             | Mean voided volume (mL) ±SD | Mean postvoid residual volume (mL) ±SD | Mean $Q_{\text{max}}$ (mL/sec) ±SD | Mean $P_{\text{det}}Q_{\text{max}}$ (cmH$_2$O) ±SD | Mean first sensation of bladder filling (mL) ±SD | Mean cystometric capacity (mL) ±SD |
|--------------------------|----------------------------|----------------------------------------|-----------------------------------|-------------------------------------------------|---------------------------------------------|-----------------------------|
| Al Timimi et al 2020 [20]| NA                         | 127±15                                 | 14±1.3                            | NA                                              | NA                                          | 426±414                     |
| Changxiao et al 2014 [21]| NA                         | 323±79.7                               | 9.6±7.1                           | 32.4±13.2                                       | 238.1±58.3                                 | 624±117.4                   |
| Gaí et al 2015 [22]     | NA                         | 12.1±14                                | 19.8±3                            | NA                                              | 165.5±55.3                                 | 380±78                      |
| Golabek et al 2012 [23] | 414.59±154.87              | 5 (0-35)**                             | 22.331±9.99                       | 40.69±22                                        | NA                                          | 447±118.95                  |
| Lee et al 2007 [24]     | 239.4±173.6                | 104.9±59.1                             | 15.2±1.2                          | NA                                              | NA                                          | NA                         |
| Lawenstein et al 2021 [25]| 327 (293-348)*             | NA                                     | 27.6±11.1                         | 22.5±10.8                                       | 139±119                                     | NA                         |
| Malik et al 2020 [26]   | NA                         | 99±46                                  | 19±15                             | 27±18                                           | 174±179                                     | 493±284                     |
| Shin et al 2016 [27]    | 274.73±131.92              | 33.24±55.63                            | 23.55±10.26                       | 26.78±15.4                                     | 173.4±75.86                                 | NA                         |
| Tai et al 2009 [28]     | 199.5±85.2                 | 74.3±30.5                              | 13.9±7.2                          | NA                                              | NA                                          | NA                         |
| Yenilmez et al 2008 [29]| NA                         | 55.4±11*                               | 24.8±1.3*                         | 34.1±1.5*                                       | 166±10*                                     | 495±23*                     |

Of 2342 patients, 1620 had urodynamic measurements and thus were included in the meta-analysis. * Data presented as median, and range in brackets; ** Data presented as median, 25th percentile (first figure in brackets), and 75th percentile (second figure in brackets). NA – data not available (not reported); $P_{\text{det}}Q_{\text{max}}$ – maximal detrusor pressure at maximal flow rate; $Q_{\text{max}}$ – maximum flow rate; SD – standard deviation.
Diabetic Women

Voided Volume

Lower voided volume in diabetes is a surprising finding, because higher voided volumes are generally expected in diabetic patients with higher fluid turnover, and even much higher volumes in autonomic neuropathy [1,5,30]. However, in diabetic patients, according to the literature [31,32], the residual urine is larger as the autonomic neuropathic bladder cannot completely empty the bladder, and there will be residue in it. On the other hand, if we add the emptied amount and the residue volume, there is a clearly higher bladder capacity in diabetic patients [31]. This phenomenon could be explained by the selection of different stages and duration of diabetes. This clinical heterogeneity is also indicated by the statistical heterogeneity.

\[ Q_{\text{max}} \text{ and } P_{\text{det}} Q_{\text{max}} \]

\( Q_{\text{max}} \) is always lower in patients with an autonomic neuropathic bladder [33] due to impaired detrusor muscle function, which agrees with our findings. A smaller voided volume always has a lower \( Q_{\text{max}} \) [34,35], but in this case the bladder also contains residual volume, and this should be taken into account during contraction, so the value is even worse.

| Study       | Total | Mean  | SD   | Mean (mL) | 95% CI  | Weight |
|-------------|-------|-------|------|-----------|---------|--------|
| Tai et al 2009 | 272   | 199.50| 85.20| 199.50    | [189.73; 209.63] | 21.0% |
| Lee et al 2007 | 47    | 239.40| 173.60| 239.40    | [189.77; 289.03] | 19.1% |
| Shin et al 2016 | 92    | 274.73| 131.92| 274.73    | [247.77; 301.96] | 20.4% |
| Løwenstein et al 2021 | 31   | 322.67| 42.75| 322.67    | [307.62; 337.71] | 20.9% |
| Golabek et al 2021 | 29   | 414.59| 154.87| 414.59    | [358.22; 470.96] | 18.6% |

Random effect model

Heterogeneity: I²=98%, p<0.01

| Study       | Total | Mean  | SD   | Mean (mL) | 95% CI  | Weight |
|-------------|-------|-------|------|-----------|---------|--------|
| Gali et al 2015 | 19    | 12.10 | 14.00| 12.10     | [5.80; 18.40] | 11.1% |
| Golabek et al 2021 | 29   | 13.33 | 27.29| 13.33     | [3.40; 23.27] | 11.1% |
| Shin et al 2016 | 92    | 33.24 | 55.63| 33.24     | [21.87; 44.61] | 11.1% |
| Yenilemez et al 2008 | 45  | 55.40 | 73.79| 55.40     | [33.84; 76.96] | 11.0% |
| Tai et al 2009 | 272   | 74.30 | 30.50| 74.30     | [70.68; 77.92] | 11.1% |
| Malik et al 2020 | 96    | 99.00 | 46.00| 99.00     | [89.80; 108.20] | 11.1% |
| Lee et al 2007 | 47    | 104.90| 59.10| 104.90    | [88.00; 121.80] | 11.1% |
| Al Timimi et al 2020 | 71  | 127.00| 15.00| 127.00    | [123.51; 130.49] | 11.1% |
| Changxiao et al 2014 | 918 | 323.00| 79.70| 323.00    | [317.84; 328.16] | 11.1% |

Random effect model

Heterogeneity: I²=100%, p<0.01

| Study       | Total | Mean  | SD   | Mean (mL/s) | 95% CI  | Weight |
|-------------|-------|-------|------|-------------|---------|--------|
| Changxiao et al 2014 | 918   | 9.60  | 7.10 | 9.60        | [9.14; 10.06] | 10.4% |
| Tai et al 2009 | 272   | 13.90 | 7.20 | 13.90       | [13.04; 14.76] | 10.3% |
| Al Timimi et al 2020 | 71    | 14.00 | 1.30 | 14.00       | [13.70; 14.30] | 10.4% |
| Lee et al 2007 | 47    | 15.20 | 1.20 | 15.20       | [14.86; 15.54] | 10.4% |
| Malik et al 2020 | 96    | 19.00 | 15.00| 19.00       | [16.00; 22.00] | 9.7% |
| Gali et al 2015 | 19    | 19.80 | 3.00 | 19.80       | [18.45; 21.15] | 10.3% |
| Golabek et al 2021 | 29    | 22.33 | 9.99 | 22.33       | [18.70; 25.97] | 9.4% |
| Shin et al 2016 | 92    | 23.55 | 10.26| 23.55       | [21.45; 25.65] | 10.0% |
| Yenilemez et al 2008 | 45  | 24.80 | 8.72 | 24.80       | [22.25; 27.35] | 9.9% |
| Løwenstein et al 2021 | 31  | 27.60 | 11.10| 27.60       | [23.69; 31.51] | 9.2% |

Random effect model

Heterogeneity: I²=99%, p<0.01

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At maximum flow, the detrusor pressure \( P_{\text{det, } Q_{\text{max}}} \) is lower in diabetes due to the dysfunction and abnormal innervation.

Lee et al [24] reports lower \( Q_{\text{max}} \) in the diabetic group without bladder dysfunction \((n = 135, \text{Q}_{\text{max}}: 19.9\pm0.7 \text{ mL/s})\), which is even more profound with bladder dysfunction \((n = 47, \text{Q}_{\text{max}}: 15.2\pm1.2 \text{ mL/s})\) compared to healthy women \((n = 197, \text{Q}_{\text{max}}: 25.8\pm8.4 \text{ mL/s})\).

**Postvoid Residual Volume, First Sensation of Bladder Filling, and Cystometric Capacity**

Autonomic neuropathy reduces the sensation of the bladder [36-38], so it is well understood that the onset of the first urge to urinate in diabetic patients occurs at higher bladder volumes.

Bladder capacity is always higher during cystometry and is markedly higher in diabetic patients [36,39].

Lee at al [24] reported that 1.6% of diabetic women had bladder capacity >500 mL and 0% in the healthy control group; 25.8% of patients had voiding dysfunction in the diabetic group and 3.5% in the healthy population; and 14.8% of diabetic patients and 1.5% of healthy people have postvoid residual >100 mL.

**Non-Diabetic Women**

Haylen et al [34] found that \( Q_{\text{max}} \) and \( Q_{\text{ave}} \) are strongly related to voided volume. Afraa et al [40] found \( Q_{\text{max}} \) values ranging between 23 and 32 mL. Wyman et al [12] included 3090

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**Figure 2. Forest plots of the urodynamic parameters of diabetic women.**

(A) Represents the pooled mean voided volume of diabetic women \((n = 471)\). (B) Shows the pooled mean postvoid residual volume of diabetic women \((n = 1589)\). (C) Demonstrates the pooled mean \( Q_{\text{max}} \) values in diabetic women \((n = 1620)\). (D) Presents the pooled mean \( P_{\text{det, } Q_{\text{max}}} \) values in diabetic women \((n = 1211)\). (E) Reveals the pooled mean first sensation of bladder filling in diabetic women \((n = 1201)\). (F) Unveils the pooled mean maximum cystometric capacity \((\text{MCC})\) in diabetic women \((n = 1178)\). Statistical analyses were carried out using R statistical software (version 4.0.5) and package "meta" (version 4.18-1).
healthy women ranging in age from 19 to 91 years from 24 studies in their meta-analysis of normative reference values for bladder function parameters. They found 334 mL [95% CI: 299-350] for mean voided volume, 12 mL [95% CI: 4-20] for mean postvoid residual volume, and 28 mL/s [95% CI: 27-30] for mean Q_{\text{max}}. Sorel et al [11] included 1416 adult patients to their systematic review. They found 338 mL [SD: 161] for mean voided volume, 23.5 mL [SD: 10] for mean Q_{\text{max}} and 15.5 mL [SD: 25] for mean postvoid residual volume. Mahfouz et al [41] found 175 mL for first sensation of bladder filling, and normal maximum cystometric capacity of 300-500 mL.

These findings agree with our results.

**Diabetic Adults with and without LUTS**

As diabetes progresses, LUTS also appears [36,42] which suggests more pronounced bladder damage, so it is understandable that in diabetes with LUTS, higher voided volumes suggest greater bladder capacity compared to diabetics without LUTS. The same more pronounced damage is indicated by increased detrusor muscle weakness in diabetic patients with LUTS compared to those without voiding symptoms. Higher detrusor pressure at maximum flow only fits into this pattern if it indicates a LUTS outflow disturbance. The rate of residual urine is higher in diabetics who also have LUTS.

**Non-Invasive Urodynamic Measurements in Routine Diabetes Follow-Ups**

Translational research takes scientific discoveries made in the laboratory and transforms them into new treatments [43]. Therefore, the sooner the early signs of DC are discovered, the earlier the therapeutic modifications can be initiated. Uroflowmetry can highlight the progressive nature of diabetes – starting with storage changes, then developing voiding dysfunction due to detrusor overdistension, to the decompensated phase. As early alterations in voiding patterns can be seen during the urodynamic examination before bothersome urinary symptoms are recognized by patients, urodynamics, mostly uroflowmetry, can contribute to early diagnosis of DC. Therefore, the inclusion of routine uroflow measurements to the current guidelines of diabetes management is crucial.

Although progression of DC is believed to be related to the duration of diabetes, and poor metabolic status; animal studies raised the question of whether changes in bladder function begin soon after its onset [43,44]. Previous studies have suggested that DC is not the prime urodynamic finding in diabetics. Kaplan et al [6] found that detrusor overactivity was the most common finding. Kebapci et al [45] came to the conclusion that classic CD occurs in only 44% of women with type 2 diabetes followed for a mean of 13.85 years; more common findings are detrusor overactivity, stress, and urge incontinence.

Although, summary mean estimates of bladder function parameters for diabetic women were calculated, heterogeneity between the studies was high for all outcomes. Therefore, this precludes generalization of these estimates to all diabetic women. Further research is needed to determine reference values within specific subgroups.

**Strength of the Study and Limitations**

To the best of our knowledge, this is the first meta-analysis that synthesizes quantitative data about urodynamic measurements of female patients with diabetes. Nonetheless, the strength of our meta-analysis is the use of a comprehensive and precise search strategy and data extraction.

The main limitation is that we could not directly compare diabetic and non-diabetic women, since there were insufficient studies directly comparing diabetic and non-diabetic patients. The lack of definition of diabetic cystopathy is also a limitation, and only 2 studies reported it [24,29].

**Conclusions**

**Implication for Practice**

Diabetes is an important independent risk factor for LUTS. Urodynamics can detect early alterations in voiding function, which might help to apply interventions to delay or prevent the onset of diabetes to limit difficulties in voiding.

Uroflowmetry may be considered in current diabetes guidelines. Regular uroflow measurements can contribute to the early recognition of DC.

**Implication for Research**

Due to the limitations, our findings should be verified by future comparative studies in people with diabetes. To carry out more accurate analyses, it is important to compare larger number of patients with different stages and duration of diabetes, with different metabolic status as well.

**Acknowledgments**

László Szabó is the guarantor of this study and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Materials

Supplementary Table 1. Search strategy of diabetes and urodynamics.

| MEDLINE                                                                                     | EMBASE                                                                                     |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 1. “urodynamic”                                                                            | 1. “urodynamic”                                                                            |
| 2. “uroflow*”                                                                              | 2. “uroflow*”                                                                              |
| 3. “uroflowmetry”                                                                          | 3. “uroflowmetry”                                                                          |
| 4. “diabetes”                                                                              | 4. “diabetes”                                                                              |
| 5. “diab*”                                                                                 | 5. “diab*”                                                                                 |
| 6. (#1 OR #2 OR #3) AND (#4 OR #5)                                                         | 6. (#1 OR #2 OR #3) AND (#4 OR #5)                                                         |

(“urodynamical”[All Fields] OR “urodynamically”[All Fields] OR “urodynamics”[MeSH Terms] OR “urodynamics”[All Fields] OR “urodynamic”[All Fields] OR “uroflow*”[All Fields] OR (“uroflowmetries”[All Fields] OR “uroflowmetry”[All Fields]) AND (“diabetes”[All Fields] OR “diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields] OR “diabetes”[All Fields] OR “diabetes insipidus”[MeSH Terms] OR (“diabetes”[All Fields] AND “insipidus”[All Fields]) OR “diabetes insipidus”[All Fields] OR “diabetic”[All Fields] OR “diabetics”[All Fields] OR “diabets”[All Fields] OR “diab*”[All Fields])

Search Date: November 4, 2021
Number of Results: 454

Cochrane Central Register of Controlled Trials (CENTRAL)

| MEDLINE                                                                                     | EMBASE                                                                                     |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 1. “urodynamic”                                                                            | 1. “urodynamic”                                                                            |
| 2. “uroflow*”                                                                              | 2. “uroflow*”                                                                              |
| 3. “uroflowmetry”                                                                          | 3. “uroflowmetry”                                                                          |
| 4. “diabetes”                                                                              | 4. “diabetes”                                                                              |
| 5. “diab*”                                                                                 | 5. “diab*”                                                                                 |
| 6. (#1 OR #2 OR #3) AND (#4 OR #5)                                                         | 6. (#1 OR #2 OR #3) AND (#4 OR #5)                                                         |

(urodynamic OR uroflow* OR uroflowmetry) AND (diabetes OR diab*)

Search Date: November 4, 2021
Number of Results: 63

Web of Science Core Collection

| MEDLINE                                                                                     | EMBASE                                                                                     |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 1. “urodynamic”                                                                            | 1. “urodynamic”                                                                            |
| 2. “uroflow*”                                                                              | 2. “uroflow*”                                                                              |
| 3. “uroflowmetry”                                                                          | 3. “uroflowmetry”                                                                          |
| 4. “diabetes”                                                                              | 4. “diabetes”                                                                              |
| 5. “diab*”                                                                                 | 5. “diab*”                                                                                 |
| 6. (#1 OR #2 OR #3) AND (#4 OR #5)                                                         | 6. (#1 OR #2 OR #3) AND (#4 OR #5)                                                         |

ALL FIELDS: ((urodynamic or uroflow* or uroflowmetry)) AND ALL FIELDS: ((diabetes or diab*))

Search Date: November 4, 2021
Number of Results: 460

Total number of records: 1750
QUIPS assess risk of bias in studies of prognostic factors.

Concerns about risk of bias and applicability were rated as “low”, “moderate” or “high” in six domains: 1) study participation, 2) study attrition, 3) prognostic factor measurement, 4) outcome measurement, 5) study confounding, as well as 6) statistical analysis and reporting.

To judge overall risk, the review authors (ÁRM and PP) described studies with a low risk of bias as those in which at least five of the six important bias domains were rated as having low risk of bias. If there was at least one domain rated as high risk, or more than three domains rated as moderate risk of bias, the overall risk of bias was deemed high. All other variations were determined as moderate risk of bias.

**Abbreviations:** QUIPS – quality in prognostic studies.

Supplementary Figure 1A. Risk of bias assessment on study level [A1] and across studies [A2] assessing mean voided volume (mL) in diabetic female population. 1: Diabetes definition and duration, as well as LUTS assessment were not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 2: Study design is not reported. Not all patients were included in the analysis, diabetes definition and treatment are not reported. 3: Definition of diabetes and type of it are not reported. 4: Type of diabetes and LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 5: Definition of diabetes is not reported.
Supplementary Figure 1B. Risk of bias assessment on study level [B1] and across studies [B2] assessing mean postvoid residual (mL) in diabetic female population. 1: HgA1c, diabetes duration are not reported. The measuring method of postvoid residual volume is not reported. The method (device) of the uroflowmetry parameters is not reported. Although it is reported that diabetes treatment was evaluated, but data could not be extracted. Statistical analysis is not reported. 2: Not all patients were included in the analysis. The measuring method of postvoid residual volume is not reported. Assessed confounding factor is caused by unreported BMI. 3: The study design is unknown, and not all patients were included in the analysis. The measuring method of postvoid residual volume is not reported. Diabetes definition is not reported. 4: Diabetes definition and duration, as well as LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 5: Study design is not reported. Not all patients were included in the analysis. Diabetes definition and treatment are not reported. 6: Type of diabetes and definition of it, as well as LUTS assessment are not reported. Diabetes treatment is partly reported. 7: Type of diabetes and LUTS assessment are not reported. The measuring method of postvoid residual volume is not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 8: Diabetes definition is not reported. 9: Not all patients were included in the analysis. Diabetes definition and LUTS assessment are not reported. Existence of pyuria is a confounding factor. Diabetes treatment is partly reported.
Supplementary Figure 1C. Risk of bias assessment on study level [C1] and across studies [C2] assessing mean Qmax (mL/sec) in diabetic female population. 1: HgA1c, diabetes duration are not reported. The method (device) of the uroflowmetry parameters is not reported. Although it is reported that diabetes treatment was evaluated, but data could not be extracted. Statistical analysis is not reported. 2: Not all patients were included in the analysis. Assessed confounding factor is caused by unreported BMI. 3: The study design is unknown, and not all patients were included in the analysis. The measuring method of postvoid residual volume, as well as diabetes definition are not reported. 4: Diabetes definition and duration, as well as LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI; and patients having Qmax lower than 12 mL/min were excluded. 5: Study design is not reported. Not all patients were included in the analysis. Diabetes definition and treatment are not reported. 6: Definition of diabetes and type of it are not reported. 7: Type of diabetes and definition of it, as well as LUTS assessment are not reported. Diabetes treatment is partly reported. 8: Type of diabetes and LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 9: Definition of diabetes is not reported. 10: Not all patients were included in the analysis. Diabetes definition and LUTS assessment are not reported. Existence of pyuria is a confounding factor. Diabetes treatment is partly reported.
### Supplementary Figure 1D

Risk of bias assessment on study level [D1] and across studies [D2] assessing mean $P_{\text{det}}^\text{Q}_{\text{max}}$ (cmH$_2$O) in diabetic female population.

1. Not all patients were included in the analysis. Assessed confounding factor is caused by unreported BMI.
2. Diabetes definition and duration, as well as LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI.
3. Definition of diabetes and type of it are not reported.
4. Type of diabetes and definition of it, as well as LUTS assessment are not reported. Diabetes treatment is partly reported.
5. Type of diabetes and LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI.
6. Not all patients were included in the analysis. Diabetes definition and LUTS assessment are not reported. Existence of pyuria is a confounding factor. Diabetes treatment is partly reported.
Supplementary Figure 1E. Risk of bias assessment on study level [E1] and across studies [E2] assessing mean first sensation (mL) in diabetic female population. 1: Not all patients were included in the analysis. Assessed confounding factor is that BMI was not reported. 2: The study design is unknown, and not all patients were included in the analysis. Diabetes definition is not reported. 3: Definition of diabetes and type of it are not reported. 4: Type of diabetes and definition of it, as well as LUTS assessment are not reported. Diabetes treatment is partly reported. 5: Type of diabetes and LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 6: Not all patients were included in the analysis. Diabetes definition and LUTS assessment are not reported. Existence of pyuria is a confounding factor. Diabetes treatment is partly reported.
Supplementary Figure 1F. Risk of bias assessment on study level [F1] and across studies [F2] assessing mean cystometric capacity (mL) in diabetic female population. 1: HgA1c, diabetes duration are not reported. The method (device) of the uroflowmetry parameters is not reported. Although it is reported that diabetes treatment was evaluated, but data could not be extracted. Statistical analysis is not reported. 2: Not all patients were included in the analysis. Assessed confounding factor is caused by unreported BMI. 3: The study design is unknown, not all patients were included in the analysis. Diabetes definition is not reported. 4: Diabetes definition and duration, as well as LUTS assessment are not reported. Assessed confounding factors are caused by unreported treatment of diabetes and BMI. 5: Type of diabetes and definition of it are not reported. LUTS assessment is not reported. Diabetes treatment is partly reported. 6: Not all patients were included in the analysis. Diabetes definition and LUTS assessment are not reported. Existence of pyuria is a confounding factor. Diabetes treatment is partly reported.
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