The role of urodynamics detecting neuropathic bladder dysfunction in non-urological diseases

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Ph.D. Thesis

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I. PUBLICATIONS

1.1. Publications related to the subject of the thesis

I. **Martonosi ÁR,** Pázmány P, Kiss S, Dembrovszky F, Oštarijaš E, Szabó L.
Urodynamics in Early Diagnosis of Diabetic Bladder Dysfunction in Women: A Systematic Review and Meta-Analysis.
MED SCI MONIT. 2022 Jul 9;28:e937166.
doi: 10.12659/MSM.937166. PMID: 35808810; PMCID: PMC9278270.
Q2, IF: 3.386

II. **Martonosi ÁR,** Pázmány P, Kiss S, Földi M, Zsákai A, Szabó L.
Urine flow acceleration in healthy children: A retrospective cohort study.
NEUROUROL URODYN. 2023 Feb;42(2):463-471.
doi: 10.1002/nau.25123. Epub 2022 Dec 27. PMID: 36573908.
D1, IF: 2.367

III. **Martonosi ÁR**, Pázmány P, Kiss S, Zsákai A, Szabó L.
INvesTigating the Abnormality of detrusor ConTractility by uroflowmetry in diabetic children (INTACT Trial): protocol of a prospective, observational study.
BMJ OPEN. 2022 Nov 14;12(11):e062198.
doi: 10.1136/bmjopen-2022-062198. PMID: 36375985; PMCID: PMC9664277.
Q1, IF: 3.007

1.2. Publications not closely related to the subject of the thesis

I. **Ágnes Rita Martonosi,** Piroska Pázmány, Márió Mikóczi, Diana Molnár, Zsuzsanna Zsófia Szalai, László Szabó. Necrotizing fasciitis and toxic shock syndrome due to Streptococcus pyogenes in a female adolescent – A case report. **J Pediatr Surg Case Rep.** 2023 March;90:102582 doi:10.1016/j.epsc.2023.102582
Q3, IF:-

II. **Martonosi ÁR**, Pázmány P, Fukász Á, Rudolf J, Kovács É, Szakács Z, Szabó L. Differential Diagnostic Challenges in the COVID-19 Pandemic: Renal Abscess After SARS-CoV-2 Infection in a Young Adolescent. **Am J Case Rep.** 2022 Mar 13;23:e935190. doi: 10.12659/AJCR.935190. PMID: 35279666; PMCID: PMC8928230.
Q3, IF:-

III. **Martonosi ÁR**, Soós A, Rumbus Z, Hegyi P, Izsák V, Pázmány P, Imrei M, Váncsa S, Szakács Z, Párniczky A. Non-invasive Diagnostic Tests in Cystic Fibrosis-Related Liver Disease: A Diagnostic Test Accuracy Network Meta-Analysis. **Front Med (Lausanne).** 2021 Jul 27;8:598382. doi: 10.3389/fmed.2021.598382. PMID: 34386504; PMCID: PMC8353091.
Q1, IF: 5.058

IV. Veres Klára, Gál Andrea Izabella, Szabó András, Szentirmai Réka, Zsigmond Borbála, **Martonosi Ágnes Rita**, Szalai Zsuzsanna Zsófia. A Heim Pál Országos Gyermekgyógyászati Intézet Bőrgyógyászatán észlelt SARS-CoV-2 infekcióval kapcsolatos esetek ismertetése és irodalmi áttekintés. **Bőrgyógyászati és Venerológiai Szemle.** 2021 97. évf. 1.36-44. doi: 10.7188/bvsz.2021.97.1.5

V. Izsák VD, Soós A, Szakács Z, Hegyi P, Juhász MF, Varannai O, **Martonosi ÁR**, Földi M, Kozma A, Vajda Z, Shaw JA, Párniczky A. Screening Methods for Diagnosing Cystic Fibrosis-Related Diabetes: A Network Meta-Analysis of Diagnostic Accuracy Studies. **Biomolecules**. 2021 Mar 31;11(4):520. doi: 10.3390/biom11040520. PMID: 33807165; PMCID: PMC8065857.

Q2, IF: 6.064

VI. Juhász MF, Varannai O, Németh D, Szakács Z, Kiss S, Izsák VD, **Martonosi ÁR**, Hegyi P, Párniczky A. Vitamin D supplementation in patients with cystic fibrosis: A systematic review and meta-analysis. **J Cyst Fibros.** 2020 Dec 18:S1569-1993(20)30940-1. doi: 10.1016/j.jcf.2020.12.008. Epub ahead of print. PMID: 33349585.
D1, IF: 5.527

VII. **Martonosi Ágnes Rita**, Scheuring Noémi, Karoliny Anna, Lőrincz Margit: Szondatáplálásra szoruló öt hónapos csecsemő táplálási zavarának kezelése. **Gyermekgyógyászat.** 2018; 69. évfolyam, 3. szám, 181-185. oldal

1.3. Scientific metrics

Number of publications **related to the subject of the thesis**: 3 (3 first author)
Cumulative impact factor of publications related to the thesis: 8.76
D1: 1, Q1: 1, Q2: 1, Q3: 0, Q4: 0

Number of **total accepted/published articles**: 10 (7 first author)
Cumulative impact factor of the published articles: 25.409
D1: 2, Q1: 2, Q2: 2, Q3: 2, Q4: 0

Number of total citations by **MTM2**: 6
6 independent

Hirsch Index: 1
MTMT ID: 10040200
https://m2.mtmt.hu/api/author/10040200/summary

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II. LIST OF ABBREVIATIONS

BMI	body mass index
CAN	cardiovascular autonomic neuropathy
CI	confidence interval
DC	diabetic cystopathy
DM	diabetes mellitus
HgA1c	haemoglobin A1c
HOGYI	Heim Pál National Pediatric Institute
INTACT Trial	INvesTigating the Abnormality of detrusor ConTractility Trial
LUT	lower urinary tract
mL	millilitre
$P_{det}Q_{max}$	maximal detrusor pressure at maximal flow rate
Q_{acc}	urine flow acceleration (Q_{max}/TQ_{max})
Q_{ave}	average flow rate
Q_{max}	maximum flow rate
QUIPS	QUality In Prognostic Studies
SE	sensitivity
SP	specificity
TQ_{max}	time to maximum flow rate

III. INTRODUCTION AND THE AIM OF THE PHD THESIS

3.1. URODYNAMICS

Urodynamic studies are functional tests that assess pressure-flow relationship of the upper and lower urinary tract. The tests provide an objective confirmation of the normal function or dysfunction of the urinary tract system, but can also be used to accurately demonstrate the effectiveness of treatments. Uroflowmetry is an essential, non-invasive, easy-to-use, widely accessible, and quick urodynamic diagnostic tool in the evaluation of voiding function.

The elements of uroflowmetry examinations are (1) voided volume (in mL), (2) voiding time (in sec), (3) maximum or peak urine flow rate (Q_{max}, in mL/sec), (4) average urine flow rate (Q_{ave}, in mL/sec), and (5) time to maximum flow rate (TQ_{max}, in sec). Acceleration of the detrusor muscle contraction (Q_{acc}) is a calculated uroflowmetry value, which is the ratio of Q_{max} and TQ_{max}, measured in mL/sec^2; and refers to the increased flow rate in a period of time from the beginning of urination to the peak value.

The relationship between Q_{max} and Q_{acc} may characterize the urinary tract dysfunction. In urinary tract obstruction, Q_{max} decreases while Q_{acc} remains normal. In bladder dysfunction caused by the impair of detrusor muscle contraction (e.g. in autonomic neuropathy), both Q_{max} and Q_{acc} decrease. Therefore, Q_{acc} (in combination with Q_{max}) might replace invasive pressure-flow studies.

3.2. NEUROPATHIES AND THEIR EFFECT ON BLADDER FUNCTION

Neuropathy is one of the most bothersome and diverse neurological conditions which is caused by damage to the nerves of peripheral nervous system. The damage can impair sensation, movement, gland, or organ function.

Diabetic neuropathy is highlighted the most by its clinical and prognostic significance which affects one third of the patients with neuropathy, although its pathomechanism still remains poorly understood. Sensory and motor peripheral neuropathies are one of the most bothersome complications of type 2 diabetes mellitus (DM), with a global prevalence of 35.78% (in Europe 48.14%) among adult patients.

Autonomic neuropathy is caused by the damage of autonomic nerves, which can manifest in cardiovascular (disturbances of heart rate, orthostatic hypotension), genitourinary (impair of

the detrusor muscle function), gastrointestinal (dysphagia, vomiting, abdominal pain, malabsorption), thermoregulatory, pupillomotor and sudomotor symptoms.

Cardiovascular autonomic neuropathy (CAN), which occurs in 2.5–90% of diabetic patients, is associated with abnormalities of vascular dynamics and heart rate control. The gold standard examinations are cardiac autonomic reflex tests, including heart rate, blood pressure and sudomotor responses. CAN may be assessed by measuring heart-rate variability, and by the five reproducible and standardised cardiovascular reflex tests described by Ewing et al in 1980.

Detrusor muscle pathology can lead to urinary retention, incontinence, or a combination of them. Diabetic cystopathy (DC) is a well-recognized urological complication of diabetic autonomic neuropathy which occurs in 25–90% of patients. It can impair the detrusor muscle function, leading to lower urinary tract (LUT) problems. The classic triad of DC is decreased bladder sensation, impaired bladder emptying with postvoid residual volume, and increased bladder capacity.

3.3. THE AIM OF THE RESEARCH AND PHD THESIS

Our hypotheses are that (1) urodynamics can provide a fine and early diagnosis of bladder dysfunction not only in urological, but also in non-urological diseases; (2) urodynamics are underused in the diagnosis of non-urological diseases (emphasising the lack of use in diabetes care in Hungary); (3) Q_{acc} has not been widely used in the diagnosis of urological diseases and not known in the diagnosis of non-urological diseases; and (4) DC is understudied compared to other diabetic complications.

Therefore, our main aim is to assess the use of urodynamics in non-urological diseases. Under the research, we were focusing on autonomic neuropathy caused by different non-urological diseases (especially DM) since recent studies suggest that uroflowmetry might determine autonomic neuropathy earlier than CAN symptoms occur. Until now, Q_{acc} was a less frequently adapted uroflowmetry parameter, but as previous studies suggest that it might indicate the deviation of detrusor muscle function earlier than other uroflowmetry parameters (e.g. Q_{max}, Q_{ave}), therefore it seems to be a better indicator of diabetic autonomic neuropathy than cardiovascular dysfunction tests (Ewing tests). Since DC can reduce the quality of life, it is urgent to be addressed before resulting in complications.

Only a few urodynamic studies have been performed in non-urological diseases so far (in particular to investigate DC). Furthermore, traditional uroflowmetry parameters (Q_{max}, Q_{ave})

are not sufficient enough to confirm autonomic neuropathy, and Q_{acc} is not widely used. Therefore, in order to prove our hypothesis, firstly we wanted to compare the urodynamic parameters of diabetic women and healthy controls, as the literature on diabetic women is scant. To do so, a meta-analysis was performed which is a well-known statistical analysis to systematically synthetize the findings of single studies.

Normative reference values of bladder function in healthy adult women and children have been widely studied, but since there is no consensus on the cut-off values of Q_{acc} which limits its use, our second aim was to establish normal ranges of urine flow acceleration in both genders by a wide range of voided volumes, in order to assess the difference of Q_{acc} values between diabetic and healthy population.

And finally, we designed a clinical trial with diabetic and healthy population to evaluate the diagnostic accuracy [sensitivity (Se), specificity (Sp), positive and negative predictive value] of uroflowmetry in the detection of autonomic neuropathy.

We believe that the results of urodynamic studies in DC and autonomic neuropathy will support the early diagnosis of autonomic neuropathy in other non-urological diseases as well.

IV. METHDOS

4.1. CHAPTER I: META-ANALYSIS

Our primary aim was to compare the urodynamic parameters of diabetic women to those of healthy women, but eligible studies according to our inclusion criteria did not provide sufficient raw data on healthy female population. 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.

The study was in line with the protocol registered on 23 May 2021 in PROSPERO (CRD42021256275).

For data synthesis we used the random-effects model with restricted maximum-likelihood estimation in all cases; means and 95% confidence intervals were calculated. The calculated effect sizes were visualized in forest plots. Heterogeneity was tested using Cochrane's Q and the I^2 statistics.

The risk of bias of the studies were evaluated by using the Quality In Prognostic Studies (QUIPS) tool. The result of the assessment was graphically demonstrated.

4.2. CHAPTER II: URINE FLOW ACCELERATION NOMOGRAMS

A single-centre, retrospective cohort study was conducted with 270 healthy children and adolescents. Eligibility criteria included healthy children aged between 6 and 18 years, without any acute or chronic disease or medicine consumption. Age (years), gender (boys/girls), weight (kg), height (cm), and uroflowmetry parameters were collected. Each child urinated multiple times (spontaneously in calm conditions, at first desire to void after 15 mL/kg liquid consumption, and at maximal sensation of bladder fullness). Uroflowmetry was performed using a Uroflow-cystometer (X0002, Metripond, Hungary) which determined Q_{max}, Q_{ave} and TQ_{max}. Voided volume (mL), voiding time (sec), Q_{max} (mL/sec), Q_{ave} (mL/sec), and TQ_{max} (sec) were measured; Q_{acc} (mL/sec^2) was calculated. Q_{max} and Q_{ave} were defined according to the International Children's Continence Society. Voided volume was measured manually using a graduated cylinder; boys voided in a standing, girls in a sitting position. Ultrasound was accomplished before and after micturition. Scans were obtained with a real time ultrasound scanner (Hitachi EUB 40.5 MHz transducer) using a direct scanning technique. Postvoid bladder diameter (mm) was measured by ultrasonography and converted to bladder residual volume (mL). Different uroflow parameters can only be compared if voided volumes are the same, since uroflow parameters highly depend on voided volumes. Therefore, children were allocated to one of the two groups by gender, and then Q_{acc} was determined by voided volumes. All descriptive statistic calculations were carried out with MS Excel [version 16.52, Microsoft Corporation (2019)]. Quantile method was used to establish the 3–97th percentile levels with SPSS (version 25.0, Armonk, NY: IBM Corporation, US) statistical software package. The centile curves of acceleration by voided volume were estimated by using lmsChartMaker Pro 2.3 (Medical Research Council, UK 1997–2006; Cole and Green 1994; Cole and Pan 2004) software based on the LMS method.

4.3. CHAPTER III: INTACT STUDY

INvesTigating the Abnormality of detrusor ConTractility Trial (INTACT) is a prospective, observational, single-centre clinical trial to evaluate the diagnostic accuracy of uroflowmetry in the detection of autonomic neuropathy.

The primary endpoint is the diagnostic accuracy (Se, Sp, negative and positive predictive values) of the uroflowmetry tests compared to the cardiovascular autonomic dysfunction

(CAD) tests in the detection of autonomic neuropathy. The secondary endpoints are (1) the existence of peripheral and autonomic neuropathy in diabetic children in parallel with the metabolic status (prevalence and incidence of peripheral and autonomic neuropathy), (2) differences in metabolic status [weight, height, body surface, body mass index (BMI), laboratory parameters, body composition], (3) fluid turnover, and (4) clinical symptoms of diabetic patients comparing to healthy children.

The protocol was approved by the local Scientific and Research Ethics Committee of the HOGYI Medical Research Council (ethical approval number KUT-37/2021). The study was registered in ClinicalTrials.gov Protocol Registration and Results System under the registration number NCT05247840 on 18 February 2022.

The inclusion criteria include children aged 5–18 years (boys and girls) with type 1, type 2 and monogenic DM who are treated at the Endocrinology Department and Outpatient Clinic of Heim Pál National Pediatric Institute (HOGYI, Budapest, Hungary) will be enrolled. Healthy volunteer children aged 5–18 years (boys and girls) without any acute or chronic disease will be enrolled in the control group, and the same tests will be performed on them as on diabetic children. The following parameters will be collected:

4.3.1. Baseline characteristics

(1) Date of birth, age (years), gender (boys/girls), race (white/black/Indian/Asian/other); (2) weight (kg), height (cm), body surface calculated by Mosteller formula, BMI and BMI percentiles; (3) diet, alcohol consumption, and smoking habits; (4) regular medicine consumption (drug active ingredient); (5) physical status, vital parameters [axillary temperature (°C), respiratory rate (respirations/min), oxygen saturation measured by pulse oximetry (%), heart rate (beats/min), non-invasive blood pressure (mmHg), and capillary refill time (sec)] will be recorded.

4.3.2. Clinical symptoms

Urge to urinate (urgency), daytime urine incontinence, nocturnal urination, nocturnal enuresis, frequency of bowel movement, and consistency of stool will be recorded.

4.3.3. Diabetes anamnesis

Type of diabetes, time of diagnosis, treatment (oral antidiabetics, diet, insulin), method of insulin administration (subcutaneous injection, pump), use of sensor–pump, the total number of diabetic ketoacidosis, haemoglobin A1c value (%), fasting glucose value (mmol/L), and postprandial glucose value (mmol/L) will be recorded.

4.3.4. Fluid balance in the past 48 hours

48-hour consumed liquid and outflow fluid flow will be documented.

4.3.5. Laboratory parameters

Urine rapid test, C reactive protein (mg/L), white blood cell count (G/L), absolute neutrophil count, absolute lymphocyte count, red blood cell count (T/L), haemoglobin (g/L and conversion: mmol/L), haematocrit (%), platelet count (G/L), glucose (mmol/L and conversion: mg/dL) blood urea nitrogen (mmol/L and conversion: mg/dL), creatinine (µmol/L and conversion: mg/dL, carbamide (mg/dL and conversion: mmol/L), estimated glomerular filtration rate (mL/min), aspartate aminotransferase/glutamic-oxaloacetic transaminase (U/L), alanine transaminase/glutamic pyruvic transaminase (U/L), gamma-glutamyl transferase (U/L), lactate dehydrogenase (U/L), alkaline phosphatase (U/L), Natrium (mmol/L), Potassium (mmol/L), Chloride (mmol/L), Calcium (mmol/L), albumin (g/L), serum total protein concentration (g/dL), and C-peptide (ng/mL) will be collected.

4.3.6. Body composition analysis

Body composition analysis (*InBody*®) – which determines the impedance by age, gender, body type or ethnicity – will be executed. Total body water, lean body mass, dry lean mass, skeletal muscle mass, and body fat mass will be measured; basal metabolic rate and body fat percentage will be calculated.

4.3.7. Uroflowmetry parameters

Uroflowmetry parameters will be recorded at spontaneous voiding and at first sensation of bladder filling after 15 mL/kg liquid consumption. Urinary bladder function will be assessed by uroflowmetry, and postvoid residual volume will be detected by ultrasonography. Q_{max}, Q_{ave}

(in mL/sec), TQ_{max} (in sec), voided volume (in mL), and voiding time (in sec) will be measured; Q_{acc} (in mL/sec^2) will be calculated. Postvoid bladder diameter (in mm) will be measured by ultrasonography and converted to bladder residual volume (in mL).

4.3.8. Cardiovascular autonomic dysfunction tests

Cardiovascular autonomic dysfunction will be assessed by the Ewing tests. During the examination, electrocardiogram and blood pressure values will be recorded continuously with the reflex tests, as well as a 1 min rhythm strip to calculate the standard deviation of the normal-to-normal interval.

4.3.9. Peripheral neuropathy examination

Peripheral neuropathy will be evaluated by a nerve conduction test. The device measures motor conduction in the lower extremities.

V. RESULTS

5.1. CHAPTER I: META-ANALYSIS

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 were used in the quantitative synthesis. Studies took place in 9 different countries, and were published between 2002 and 2020; 6 studies were prospective, 2 were retrospective cohorts, and 2 studies did not provide sufficient information about study design.
10 studies were included to the quantitative synthesis that reported on a total of 2342 diabetic patients, including 2055 patients (87.7%) with LUT symptoms. The majority of the patients had type 2 diabetes. In 7 studies, the type of diabetes was reported, while in 3 studies 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/m^2, and the mean HgA1c ranged between 6.05 ± 2.38 and 9.1 ± 2.6 %.
The pooled event rates show that mean voided volume in diabetic women (n = 471) is 288.21 mL [95% CI: 217.35–359.06] with a considerable level of heterogeneity (I^2 = 98%). The pooled event rates represent that mean postvoid residual volume in diabetic women (n = 1589) is 93.67

mL [95% CI: 31.35–155.99] with a considerable level of heterogeneity (I^2 = 100%). The mean Q_{max} in diabetic women (n = 1620) is 18.80 mL/sec [95% CI: 15.27–22.33] with a considerable level of heterogeneity (I^2 = 99%). The mean $P_{det}Q_{max}$ in diabetic female population (n = 1211) is 30.13 cmH_2O [95% CI: 25.53–34.73] with a considerable level of heterogeneity (I^2 = 90%). The mean first sensation of bladder filling in diabetics (n = 1201) is 178.66 mL [95% CI:150.59–206.72] with a considerable level of heterogeneity (I^2 = 97%). The mean maximal cystometric capacity in diabetic women (n = 1178) is 480.41 mL [95% CI:409.32–551.50] with a considerable level of heterogeneity (I^2 = 98%).

In the analysis of female diabetic patients' urodynamic parameters, the majority of the studies had high overall risk of bias. One study had moderate overall risk of bias because not all patients were included in the urodynamic analysis, and one study was reported as having low overall risk of bias.

5.2. CHAPTER II: URINE FLOW ACCELERATION NOMOGRAMS

Out of 270 healthy children, 208 were enrolled in the analysis who performed 404 micturition total. 62 children were excluded due to the following reasons: 33 children were excluded due to voided volume less than 20 mL, and 29 children were excluded due to postvoid residual volume of more than 15% of voided volume.

Out of 208 children, 94 are female and 114 are male. The mean age of the total population is 9.68 ± 3.09 years, the median weight is 32 [14–78] kg, the mean height is 138.76 ± 19.21 cm, and the mean body surface is 1.19 ± 0.28 m^2. The median voided volume is 130 [20–460] mL, the median voiding time is 10 [3–56] sec, the median TQ_{max} is 3 [1–14] sec, the median Q_{ave} is 11.7 [2.5–36.6] mL/sec, the median Q_{max} is 20.5 [5–50] mL/sec, the median Q_{acc} is 6 [0.81–25] mL/sec^2, and the median postvoid residual volume is 1.83 [0–38.62] mL.

Out of the 94 girls with 169 urinations, the mean age is 9.71 ± 2.95 years, the median weight is 32 [14–71] kg, the mean height is 138.13 ± 17.84 cm, and the mean body surface is 1.18 ± 0.27 m^2. The median voided volume is 130 [20–375] mL, the median voiding time is 10 [3–48] sec, the median TQ_{max} is 3 [1–12] sec, the median Q_{ave} is 12.5 [2.5–34] mL/sec, the median Q_{max} is 23 [5–50] mL/sec, the median Q_{acc} is 7.25 [1.12–19.5] mL/sec^2, and the median postvoid residual volume is 1.40 [0–38.62] mL.

Out of the 114 boys with 235 urinations, the mean age is 9.65 ± 3.21 years, the median weight is 32 [15–78] kg, the mean height is 139.27 ± 20.32 cm, and the mean body surface is 1.20 ±

0.29 m^2. The median voided volume is 140 [20–460] mL, the median voiding time is 10 [3–56] sec, the median TQ_{max} is 4 [1–14] sec, the median Q_{ave} is 11.11 [2.5–36.6] mL/sec, the median Q_{max} is 19 [5–50] mL/sec, the median Q_{acc} is 5.4 [0.81–25] mL/sec^2, and the median postvoid residual volume is 1.9 [0–29.10] mL.

Figure 1 and Figure 2 demonstrate the nomograms of Q_{acc} by voided volumes in girls and boys, respectively.

5.3. CHAPTER III: INTACT STUDY

The Steering Committee members will perform and analyse the examinations listed above in the *4.3.1-4.3.9. Data collection section*. Data will be handled by the Steering Committee as well.

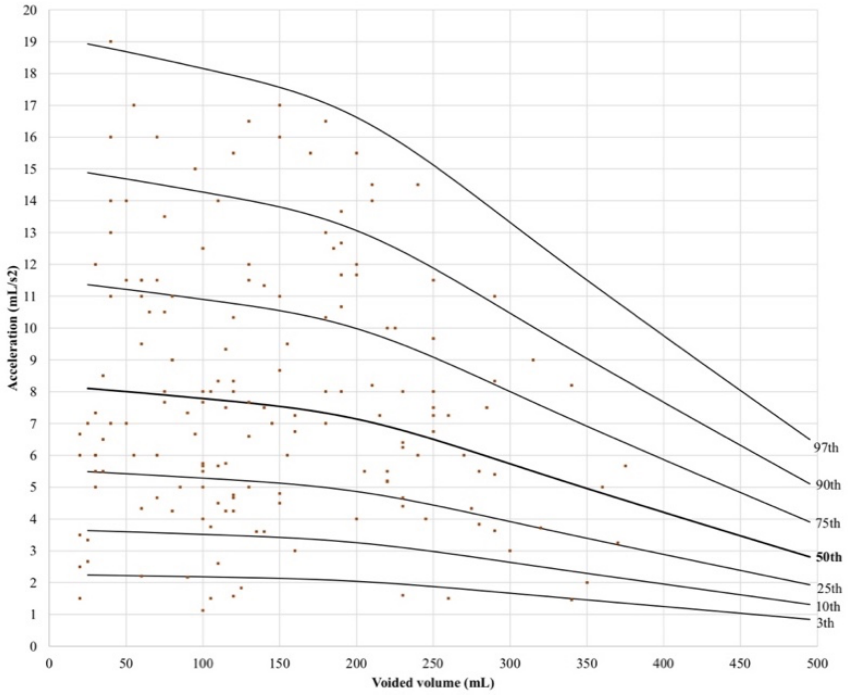

Figure 1. Urine flow acceleration (Q_{acc}) nomogram for girls

Q_{acc} is demonstrated by voided volumes in female population ≤18 years of age.

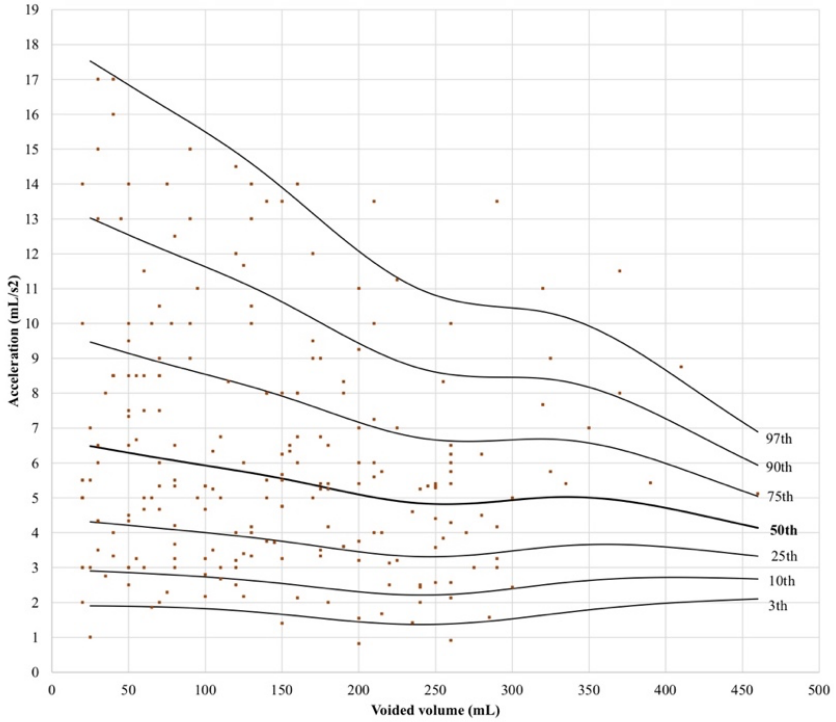

Figure 2. Urine flow acceleration (Q_{acc}) nomogram for boys

Q_{acc} is demonstrated by voided volumes in male population ≤18 years of age.

VI. DISCUSSION

6.1. CHAPTER I: META-ANALYSIS

Lower mean voided volume, Q_{max} and $P_{det}Q_{max}$; 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.

To the best of our knowledge, this is the first meta-analysis that synthetizes 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. Uroflowmetry is a non-invasive, widely accessible, quick and easy-to-use urodynamic diagnostic tool to evaluate voiding function and to determine LUT dysfunction. It might detect subtle voiding modifications in neuropathic patients before LUT symptoms manifest, therefore it seems to be a useful tool in the early diagnosis of dysfunction of the detrusor muscle. The main limitation is that we could not directly compare the parameters of diabetic and non-

diabetic women, as there were insufficient studies that directly compared these two groups of patients. The lack of definition of DC is also a limitation; only 2 studies reported it.

6.2. CHAPTER II: URINE FLOW ACCELERATION NOMOGRAMS

We have established nomograms for normative reference values of Q_{acc} in paediatric population (girls and boys separately) by voided volumes in centile forms. We have found an inversely proportional correlation between voided volumes and Q_{acc} parameters.

The diversity of Q_{acc} by percentiles is huge. We recommend that values between the 25th and 75th percentiles should be accepted as normal, which for boys is between 3.9 and 8 mL/sec^2 for a voided volume of 150 mL. If we get values below 25% or above 75%, we recommend further examinations. Theoretically, a Q_{acc} value above 75% could be caused by overactive bladder dysfunction.

Acceleration of urine flow might provide a finer diagnosis of the relationship between abnormalities of the LUT and DM as well. We believe that Q_{acc} might be used primarily to detect damage to the detrusor muscle (especially to detect reduced detrusor contraction caused by DM). We consider that Q_{acc} is a better indicator of diabetic autonomic neuropathy than CAD tests (Ewing tests), as in our previous study Q_{acc} levels were significantly decreased not only in diabetic children with CAD, but also in diabetic patients without CAD.

By the evaluation of Q_{acc}, there will be more biological indicators to assess the aetiology of the urinary problems and the effect of different diseases and treatments for voiding function to get appropriate and precise treatment for patients.

Since there are only a few studies evaluating Q_{acc} values in adults and paediatric population with different diseases; furthermore, normative reference values of Q_{acc} are lacking, we considered it important to establish normal ranges of Q_{acc} in both genders based on voided volumes in children.

The strength of this study is the novelty of the evaluation of normal reference values of Q_{acc}, which includes a relatively large number of children with Q_{acc} calculation. The main limitation of this study is the possible selection bias due to the retrospective design.

6.3. CHAPTER III: INTACT STUDY

To the best of our knowledge, this is the first prospective clinical trial evaluating early signs of neuropathy by simultaneously uroflowmetry, cardiovascular autonomic dysfunction

tests, and peripheral nerve conduction test in paediatric patients with diabetes and healthy controls.

CAN is one of the most studied forms of autonomic neuropathy, which is a frequent and early complication of diabetes, and DC is a frequent urological complication of diabetic autonomic neuropathy. Although progression of DC is believed be related to the duration of diabetes and poor metabolic status; animal studies raised the question whether changes in the bladder function begin to occur soon after its onset. Therefore, the sooner the early signs of DC are discovered, the earlier the therapeutic modifications can be initiated (tight glycaemic control), which can improve the quality of life. 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 urodynamic examinations before bothersome urinary symptoms are recognized by patients, urodynamics, mostly uroflowmetry, can contribute to the early diagnosis of DC. Therefore, the inclusion of routine uroflow measurements in the current guidelines of diabetes management is crucial.

VII. CONCLUSIONS

Urodynamic tests were primarily invented for the investigation of diseases of the lower urinary tract, but there is a rising number of data that they can be used in non-urological diseases as well. They can be used to detect and monitor the progression of the diseases and even as screening tests. Uroflowmetry is a non-invasive, widely accessible, quick and easy-to-use urodynamic diagnostic tool to evaluate voiding function and to determine LUT dysfunction. 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 might detect subtle voiding modifications in neuropathic patients before LUT symptoms manifest, and it might be a useful tool in the early diagnosis of dysfunction of the detrusor muscle. Therefore, the use of uroflowmetry may be considered in current diabetes guidelines, and regular uroflow measurements can contribute to the early recognition of DC.

Normal reference values for urinary flow acceleration were established in percentile forms in children. As acceleration of urine flow can provide a finer diagnosis of abnormalities of the LUT and various chronic diseases (DM etc.), our results could form a basis on studies about

the diagnostic significance of uroflow parameters in different non-urological diseases in children. As soon as studies – comparing the Q_{acc} values of healthy children and patients with different diseases – identify diagnostic cut-off values, the use of the normal reference values of Q_{acc} can be easily translated to everyday clinical practice. According to the currently available literature, Q_{acc} is an important tool in the diagnosis of LUT symptoms. By establishing normative reference values, interpreting the different Q_{acc} parameters might help clinicians to assess different diseases. Since we evaluated the Q_{acc} patters of healthy asymptomatic paediatric population, we formed the basis of future prospective studies. Further prospective studies comparing healthy children and paediatric population of different diseases with or without LUT symptoms will be needed to establish cut-off values to differentiate normal and abnormal uroflow patterns (voided volume, voiding time, Q_{ave}, $Q_{max,}$ TQ_{max}) as well.

In the INTACT Trial, by simultaneously assessing uroflowmetry, cardiovascular autonomic dysfunction tests, and peripheral nerve conduction test in paediatric patients with diabetes and healthy controls, diagnostic accuracy of uroflowmetry can be evaluated in the detection of neuropathy.

VIII. AUTHOR'S OWN CONTRIBUTION

8.1. MARTONOSI ET AL: MEDICAL SCIENCE MONITOR, 2022

The author studied the available literature, and performed the database search, as well as read the articles for eligibility, collected the data from the articles to the study database, performed the bias analysis and quality assessment, and completed the PRISMA checklist. The author drafted the majority of the manuscript and edited the tables and figures.

8.2. MARTONOSI ET AL: NEUROUROLOGY AND URODYNAMICS, 2023

The author studied the available literature and designed a part of the study, performed the majority of the acquisition of data, and part of the statistical analysis. The author drafted the majority of the manuscript and edited the tables and figures.

8.3. MARTONOSI ET AL: BMJ OPEN, 2022

The author studied the available literature, played a key role in the study design, wrote the majority of the manuscript and edited the study figures and tables.

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