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INvesTigating the Abnormality of detrusor ConTractility by uroflowmetry in diabetic children (INTACT Trial): protocol of a prospective, observational study

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ABSTRACT

Introduction Bladder emptying abnormalities and cardiovascular autonomic dysfunction are manifestations of autonomic dysfunction in people with diabetes mellitus (DM), which are major causes of morbidity and mortality. Since they can reduce the quality of life, they are urgent to be addressed before resulting in complications. As uroflowmetry might determine autonomic neuropathy earlier than cardiovascular autonomic dysfunction symptoms occur, our aim is to detect early abnormalities in bladder muscle function in children with DM. We investigate the diagnostic accuracy of uroflowmetry. As a secondary aim, we compare the prevalence of uroflowmetry abnormalities to the appearance of measures of cardiovascular autonomic neuropathy. Finally, as an ancillary study, we examine the association of uroflowmetry with the appearance of peripheral neuropathy. These three aims, we feel, will put our results regarding uroflowmetry into an overall context of nerve disease early in the course of type 1 DM. To our knowledge, such an approach has heretofore not been performed.

Methods and analysis This will be a prospective, observational, single-centre clinical study. Patients with DM fulfilling the inclusion criteria and healthy controls will have uroflowmetry examination, cardiovascular autonomic dysfunction tests (heart rate response to deep breathing, to Valsalva manoeuvre, blood pressure and heart rate response to standing up, and to sustained handgrip) and nerve conduction test. The autonomic nervous system function will be examined by the reproducible and standardised cardiovascular reflex tests described by Ewing *et al*. During the examination, electrocardiogram (ECG) and blood pressure values will be recorded continuously. Heart rate response to deep inspiration will be executed to investigate the parasympathetic nervous system. Peripheral neuropathy will be evaluated by nerve conduction test. After a pilot period, when the first 50 diabetic and 50 healthy children will be assessed, sample size calculation will be carried out. The primary objective of this trial is to evaluate the diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) of uroflowmetry. To do so, we compare uroflowmetry to the gold standard neuropathy tests, which are cardiovascular autonomic dysfunction tests (heart rate response to deep breathing, to Valsalva manoeuvre, blood pressure and heart rate response to standing up and to sustained handgrip).

Ethics and dissemination Ethics approval was obtained from the Scientific and Research Ethics Committee of the Heim Pál National Paediatric Institute in Budapest, Hungary (registration number KUT-37/2021). Results will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT05247840.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Assessment of metabolic status, autonomic and peripheral neuropathy simultaneously in diabetic children.
⇒ Selection of the widest possible paediatric age group (5–18 years) who can cooperate in performing the tests.
⇒ There are no drugs used in the study; therefore, no adverse and serious adverse events are expected.
⇒ Compliance is expected to be worse among younger study participants.
⇒ Uroflowmetry examinations might have potential confounding factors ((1) uroflow values are highly dependent on voided volumes; (2) psychological excitement can affect the sensation of bladder fullness, and thus voided volumes).

INTRODUCTION

Diabetes and urological problems are common and have a prominent effect on the quality of life. Autonomic neuropathy, a major cause of morbidity and mortality in diabetes, can manifest in genitourinary, cardiovascular, gastrointestinal and sudomotor symptoms etc.[1]

Diabetic cystopathy (DC), the most common urological complication of diabetic autonomic neuropathy[2] occurs in 25%–90%

of patients.[3] It can impair the detrusor muscle function, leading to lower urinary tract (LUT) problems.[4 5] The classic triad of DC is decreased bladder sensation, impaired bladder emptying and increased bladder capacity causing overactive bladder, urge or overflow incontinence and nocturia.[6–11] Assessment of DC includes urodynamic measurements[12] and LUT symptoms questionnaires.[13]

Cardiovascular autonomic neuropathy (CAN), which occurs in 2.5%–90% of patients with diabetes,[14] is associated with abnormalities of vascular dynamics and heart rate control. The clinical symptoms might vary from tachycardia, orthostasis to myocardial infarction.[14] Diagnosis is based on sympathetic and vagal autonomic function examinations. The gold standard tests are cardiac autonomic reflex tests, including heart rate, blood pressure and sudomotor responses.[15]

Recent studies suggest that uroflowmetry might determine autonomic neuropathy earlier than CAN symptoms occur.[16–18] Since DC can reduce the quality of life, it is urgent to be addressed before resulting in complications.

Uroflowmetry is a non-invasive, widely accessible, quick and easy-to-use urodynamic diagnostic tool to evaluate voiding function[19] and to determine LUT dysfunction. As uroflowmetry might detect subtle voiding modifications in neuropathic patients before LUT symptoms manifest,[16] it might be a useful tool in the early diagnosis of dysfunction of the detrusor muscle.

In addition to autonomic neuropathy, peripheral neuropathy is 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.[20] The most common form of it is symmetric generalised polyneuropathy which is a well-known microvascular complication of type 2 DM.

Since the diagnosis of autonomic and peripheral neuropathy is complex and might be inconvenient for children, our aim is to detect early abnormalities in bladder muscle function in diabetic children in an easy and painless way before the manifestation of autonomic or peripheral neuropathy.

The main objective of this trial is to evaluate the diagnostic accuracy (sensitivity (SE), specificity (Sp), positive and negative predictive value) of uroflowmetry. To do so, we compare uroflowmetry to the gold standard neuropathy tests, which are cardiovascular autonomic dysfunction tests (heart rate response to deep breathing, to Valsalva manoeuvre, blood pressure and heart rate response to standing up and to sustained handgrip) and in parallel, we evaluate peripheral nerve conduction test in diabetic children and healthy controls.

METHODS AND ANALYSIS

Study design

It is a prospective, observational, single-centre clinical trial. The study protocol is constructed in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 Statement[21]; for the checklist, see online supplemental file 1.

Patient enrolment

Inclusion criteria

Patients with diabetes

Children aged 5–18 years (boys, girls) with type 1, type 2 and monogenic DM who are treated at the Endocrinology Department and Outpatient Clinic of Heim Pál National Paediatric Institute (HOGYI, Budapest, Hungary) will be enrolled. The definition of diabetes is based on the American Diabetes Association criteria.[22]

Healthy controls

Healthy volunteer children aged 5–18 years (boys and girls) without any acute or chronic disease will be enrolled and the same tests will be performed on them as on diabetic children. Control subjects will be recruited by the HOGYI's Volunteer Recruiting Programme in kindergartens and schools.

Exclusion criteria

Patients with diabetes

Diabetic children with the following conditions will be excluded from the study:

1. Acute febrile condition (≥38°C core temperature) in the past 7 days.
2. Acute or chronic urinary tract or kidney disease: renal insufficiency (GFR ≤60 mL/min per 1.73 m^2[23]), urinary tract infection.
3. Urological disease: bladder cancer, urolithiasis, urethral stricture, posterior urethral valve, meatal stenosis, previous genitourinary surgery, conditions causing urinary outflow problems (phimosis, hypospadias, vesicoureteral reflux).
4. Cystic fibrosis-related diabetes.
5. Neurological disorders (multiple sclerosis, transient ischaemic attack, transverse myelitis, myelocele, meningomyelocele, previous spinal cord operation, or operation which might injure the sacral nerve plexus).
6. Medicines taken which can cause neuropathy[24]:
   - Cytostatic agents: cyclophosphamide, platinum-based antineoplastic agents, vinca alkaloids, epothilones, taxanes, proteasome inhibitors and immunomodulatory drugs.[25]
   - Immunosuppressive agents: TNF-alfa inhibitors (adalimumab, infliximab, etanercept), interferon.
   - Cardiovascular medicines: statins, digoxin, amiodaron.
   - Antimicrobial agents: nitrofurantoin, linezolid, voriconazole, itraconazole, antituberculotics, metronidazole, fluoroquinolone.
   - Antiulcerative agent: cimetidin.
   - Neuropsychological agents: levodopa, phenytoin.
7. Psychiatric disorders that prevent participation/collaboration in the study.

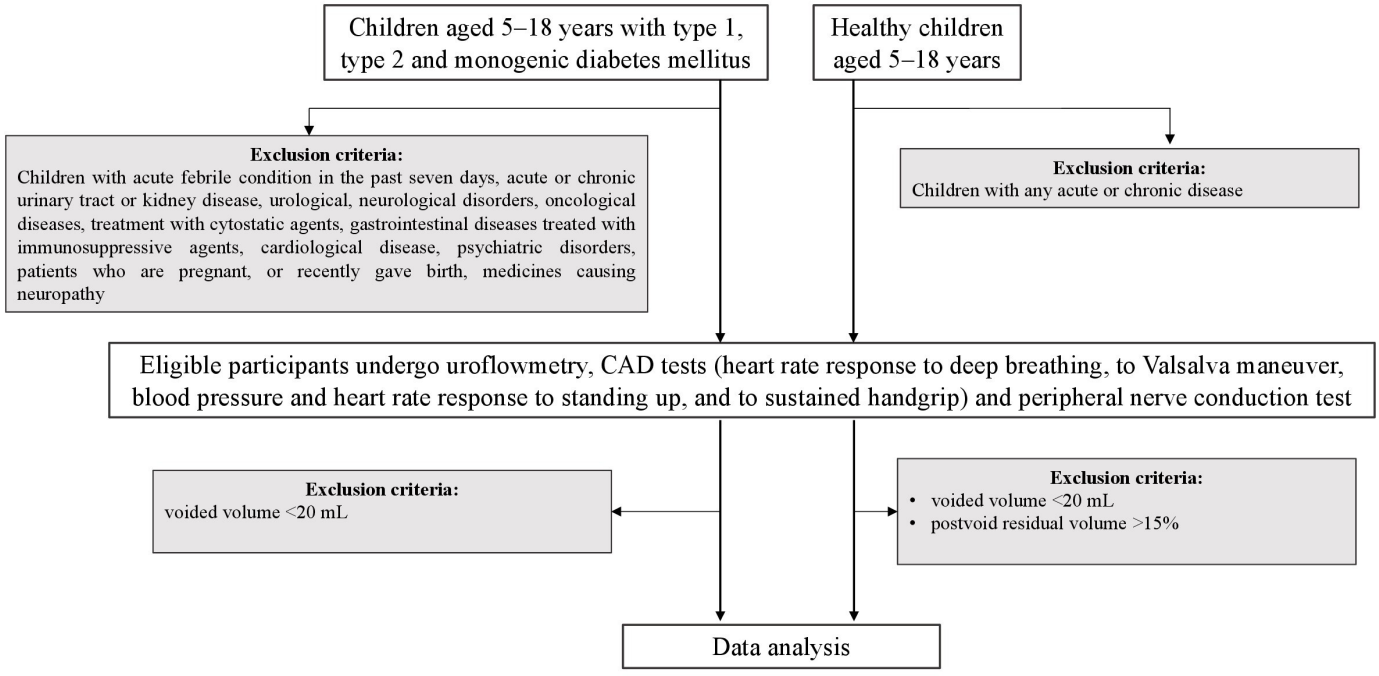

Figure 1 Flow chart of the participants according to the SPIRIT 2013 statement. CAD, cardiovascular autonomic dysfunction; SPIRIT, Standard Protocol Items: Recommendation for Interventional Trials.

8. Constipation (defined according to the Rome IV criteria[26]).
9. Voided volume <20 mL.
10. Patients who are pregnant or gave birth in the last 12 months.
11. Lack of consent of the patient or legal representative; the patient or legal representative withdraws his or her voluntary consent during the study.

Healthy controls

Children with voided volume <20 mL, and postvoid residual volume >15% will be excluded.

All patients who meet the inclusion criteria will be informed of the possibility of taking part in the INvesTigating the Abnormality of detrusor ConTractility Trial. Informed consent will be signed by the patient, or in the event of incapacitated status, by the patient's legal guardian; for details, see online supplemental file 2. The consent will be obtained by the steering committee (SC) members. Those enrolled in the study will be monitored yearly regardless they reach the age limit of 18 years during the recruitment period. The flow chart of the participants according to the SPIRIT 2013 statement is demonstrated in figure 1.

Patient and public involvement

Patients will be involved in the design and conduct of this research. During the feasibility stage, the priority of the research question, choice of outcome measures, methods of recruitment and the trial will be informed by a discussion with patients and the patient's legal guardian through a focus group session and a structured interview. Once the trial is published, participants will be informed of the results through a consultation.

Data collection

The questionnaire used in the study is shown in online supplemental file 3.

Baseline characteristics

All parameters below will be recorded:

1. Date of birth, age (years), gender (boys/girls), race (white/black/Indian/Asian/other).
2. Weight (kg), height (cm) and body surface calculated by Mosteller formula,[27] body mass index (BMI) and BMI percentiles.
3. Diet, alcohol consumption, 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 oxymetry, heart rate (beats/min), non-invasive blood pressure (mm Hg) and capillary refill time (sec)).

Clinical symptoms

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

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, hemoglobin

A1C value (%), fasting glucose value (mmol/L), postprandial glucose value (mmol/L).

Fluid balance in the past 48 hours

Documentation of 48-hour consumed liquid and outflow fluid flow.

Laboratory parameters

Urine rapid test (Medi-Test Combi 9+leuko), 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), Sodium (mmol/L), Potassium (mmol/L), Chloride (mmol/L), Calcium (mmol/L), albumin (g/L), total protein concentration (g/dL) and C-peptide (ng/mL) will be collected. Cut-off values will be determined by the Department for Laboratory Medicine of HOGYI, Budapest, Hungary.

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, and basal metabolic rate and body fat percentage will be calculated. The device will be calibrated according to the prescribed instructions for use by a skilled technician.

Uroflowmetry parameters

Uroflowmetry parameters will be recorded at spontaneous voiding and at the 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 (SonoSite M Turbo). Uroflowmetry will be performed using a uroflow-cystometer (UroDoc Frytech), which determines Q_{max}, Q_{ave} and TQ_{max}. Voided volume (in mL), voiding time (in sec), average and maximum urinary flow rate (Q_{ave} and Q_{max} in mL/s), and time to maximum urinary flow (TQ_{max} in s) will be measured; urine flow acceleration (Q_{acc} in mL/s^2) will be calculated. Q_{max} and Q_{ave} are defined according to the International Children's Continence Society.[28] The voided volume will be measured by the uroflow-cystometer device; boys void in a standing, girls in a sitting position. Postvoid bladder diameter (mm) will be measured by ultrasonography and converted to bladder residual volume (mL). The device will be calibrated according to the prescribed instructions for use by a skilled technician. The examinations will take approximately 10 min.

Cardiovascular autonomic dysfunction tests

Cardiovascular autonomic dysfunction will be assessed by five reproducible and standardised cardiovascular reflex tests described by Ewing *et al*. Three of the five tests assess parasympathetic function: heart rate response to deep breathing, to standing and the Valsalva manoeuvre. Two tests evaluate sympathetic function, which are blood pressure responses from lying to standing and at sustained handgrip. Each of these five tests is assigned a score of 0 for normal, 0.5 for borderline and 1 for abnormal results. The sum of these 5 scores—which is the Ewing score—is used to assess the severity of cardiovascular autonomic dysfunction. Patients with an Ewing score ≥2 form the cardiovascular autonomic dysfunction+group, and those with less than 2 form the cardiovascular autonomic dysfunction—group.[14 15 29–31]

During the examination, ECG and blood pressure values will be recorded continuously with the reflex tests, as well as a 1 min rhythm strip to calculate the SD of the normal-to-normal interval.

ECG recording will be executed using 1, 6 and 12 leads. The captured ECG will be taken from a recording it creates a moment and from the amount of data stored in 1 min, averaged default value calculation is implemented as the followings: mean heart rate, heart rate distribution, P wave duration, PR and RR interval, QRS duration, ST segment, QT duration, corrected QT interval (QTc) according to the Bazett's formula. Normative values will be reported on the ECG record, as well as the heart rate of the patient. The characteristics of cardiovascular autonomic dysfunction tests are demonstrated in table 1.

Peripheral neuropathy examination

Peripheral neuropathy will be evaluated by a nerve conduction test. The device measures motor conduction in the lower extremities. It operates at two dedicated frequencies in order to perform a thick myelin sheath cordless fibre (5 Hz) and thin myelinated nerve fibre (2000 Hz) examination. The device will be calibrated according to the prescribed instructions for use by a skilled technician.

The duration of the cardiovascular autonomic dysfunction examinations is about 15–20 min, and the peripheral neuropathy examination (based on the patient's attention) takes 5–10 min per limb.

Recruitment period

Recruitment period of the entire study: the planned starting date of the study is March 2022, and the planned completion date is March 2028. During the first year period, all the previously diagnosed and treated patients with diabetes, as well as the newly diagnosed ones, will be examined. The metabolic status will be evaluated in parallel with autonomic and peripheral neuropathy. After this period patients will be followed up for 5 years (regardless they reach the age of 18 years), and the same

Table 1 Characteristics of the cardiovascular autonomic dysfunction tests

Name of the cardiovascular test	Characteristics of the test	Autonomic nerve system
Heart rate response to deep breathing	The child breathes deeply in a sitting position. The maximum and minimum heart rates during each breathing cycle are measured, and the mean of the differences during three successive breathing cycles are taken to give the maximum-minimum heart rate.	Parasympathetic function
Heart rate response to standing up	The child lies on a couch and then stands up unassisted. An immediate increase in heart rate happens immediately, maximal amount is at about the 15th beat after starting to stand, followed by a relative bradycardia, maximal around the 30th beat. This will be calculated as the 30:15 ratio, which means the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.	Parasympathetic function
Valsalva manoeuvre	The child blows into a mouthpiece at a pressure of 40 mm Hg for 15 s. Normally the heart rate increases, followed by a rebound bradycardia. During the manoeuvre, the ratio of the longest and shortest R-R interval will be measured. The Valsalva ratio will be calculated as the mean ratio from three consecutive Valsalva manoeuvres.	Parasympathetic function
Blood pressure response to standing up (orthostatic hypotension)	The blood pressure (in mm Hg) is measured in a lying and standing position using a blood pressure metre (Omron M2 Intellisense). The difference in systolic blood pressure is considered to be the extent of the change in postural blood pressure. Systolic pressure is considered to be abnormal when a fall >20 mm Hg after standing up is observed.	Sympathetic function
Blood pressure response to sustained handgrip	Handgrip is maintained at 30% of the maximum voluntary contraction using a handgrip dynamometer up to a maximum of 5 min, and the blood pressure is measured each minute. The difference between the diastolic blood pressure just before the release of the handgrip, and before starting, is taken as the measure of response.	Sympathetic function

tests will be performed on the same individuals who were previously enrolled in the study, and all data (listed in the Data collection section) will be collected from them. During the 5-year follow-up period, data will be regularly collected every year. The follow-up will be continued even if we find abnormalities either in the peripheral or autonomic neuropathy examinations.

Withdrawal of a subject from the study

Patients will not be included in the per-protocol analysis if: (1) during the trial any exclusion criteria meet and (2) data required for the primary endpoints are missing.

Sample size calculation and power analyses

The trial will start with a pilot period when the first 50 diabetic and 50 healthy children will be assessed. This will be followed by a short evaluation period, during which the principal investigator and the study team could make adjustments to the study protocol to ensure feasibility. Based on the preliminary data of the pilot period, the investigators plan to carry out a sample size calculation in order to decide the timing of the interim analyses. Based on the estimated number of items, auditing trial conduct is planned after the first year and every year, on the basis which the SC will suggest changes if necessary.

Data analysis plan and outcomes

The primary endpoint is the diagnostic accuracy (SE, Sp, negative and positive predictive values) of the uroflowmetry test compared with the cardiovascular autonomic dysfunction tests in the detection of autonomic neuropathy. The secondary endpoints are the existence of peripheral and autonomic neuropathy in diabetic children in parallel with the metabolic status (prevalence and incidence of peripheral and autonomic neuropathy), differences in metabolic status (weight, height, body surface, BMI, laboratory parameters, body composition), fluid turnover and clinical symptoms of patients with diabetes comparing to healthy children.

All descriptive statistic calculations and analyses will be carried out with MS Excel (V.16.52, Microsoft Corporation (2019) and SPSS (V.24, IBM). Results will be characterised as either false positive, true positive, false negative or true negative. Using these data, sensitivities, specificities and ORs will be calculated. Basic statistical parameters, that is, mean, SD, SE of the mean, median, minimal and maximum values of the variables for the groups of diabetic children and members of the control groups, will be estimated. The centile distribution of the variables will be estimated by using lmsChartMaker Pro V.2.3 software (Medical Research Council, UK 1997–2006) based on the LMS method.[32 33] First, in the statistical analysis, we will measure the values of the above listed and detailed examinations (see Clinical symptoms–Peripheral neuropathy examination sections) and evaluate whether there is a significant difference between patients with diabetes and healthy controls: in the case of continuous variables Student's t-test and analysis of variance analysis for normally distributed variables, while Mann-Whitney U and Kolmogorov-Smirnov tests in the case of not normally distributes variables; furthermore χ^2 analysis will be used for testing distributions' homogeneity in the case of variables having discrete probability distribution. The statistical relationship and association between the variables will be tested by correlation, regression and contingency table analyses and Kendall's tau test. Univariate and multivariate analyses will be performed to assess the prognostic variables that affect the urinary bladder functions of diabetic children. As a second phase of the analysis, after

executing basic and comparative statistical analyses of the studied variables, the best cut-off values will be determined to differentiate early neuropathy from healthy controls (by estimating SE, Sp, positive and negative predictive value, likelihood ratio positive, likelihood ratio negative and characteristic of receiver operative curves). In the third phase, we will assess the diagnostic accuracy of each diagnostic test to differentiate early neuropathy (by estimating SE, Sp, predictive values, likelihood ratios, area under the receiver operating characteristic curve, overall accuracy and diagnostic OR). Significance will be set at p=0.05 level in the statistical analyses. We are not planning any statistical methods to handle missing data; data imputation will not be carried out. For each endpoint, a data quality table will be created in order to assess the extent of the potential bias provided by the missing data.

For dividing children into nutritional status subgroups, age-dependent cut-off values will be used. The following subgroups will be made during statistical analyses: (1) ages (5–9, 10–14, >14 years); (2) BMI (BMI percentiles and <18.5, 18.5–25, 25–30, 30–35, >35 kg/m^2, respectively, at the age 18 years); (3) type of diabetes (type 1, type 2, monogenic DM); (4) time of diagnosis (<5, 6–9, >10 years); (5) treatment (oral antidiabetics, diet, insulin); (6) method of insulin administration (subcutaneous injection, pump) and (7) number of total diabetic ketoacidosis (0–1, 2–5, 6–9, >10 x); (8) HgA1c value (<5.7, 5.7–6.4, >6.4%).

ETHICS AND DISSEMINATION

Ethical and legal considerations

The study will be conducted following the Declaration of Helsinki. It will be managed in compliance with the study protocol, Good Clinical Practice, designated standard operating procedures, and Hungarian laws and regulations. This protocol, in its current version, 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.

Safety monitoring plan, trial administrative organisation, committees and boards

The corresponding centre and designer of the trial is the HOGYI, Budapest, Hungary. The study was designed by the SC and Independent Expert Committee (IEC).

The SC will be led by LS (principal investigator, paediatrician and specialist in nephrology and urodynamics). SC members will be: ÁRM (paediatrician), PP (physician) and SK (physician). Primary supervision of the study will be provided by the SC; it will make decisions concerning all important questions (eg, premature termination of the study, drop-outs during the study). All recommendations will be filed. SC serves as a data monitoring committee as well. If the study expands to multicentric, so does the number of SC members.

The IEC will include two paediatric endocrinologists (ZsV and ZsA), a paediatric neurologist (BR), a paediatric oncologist (GyP) and a paediatric gastroenterologist (AK). The task of the IEC is to monitor the trial regularly, to improve adherence to the protocol and to provide recommendations to the SC. An early quality assessment check will be performed on the first 50 patients. The IEC will perform an independent assessment of the trial-related documents and activities, with the aim of ensuring the respect of subjects' rights, safety and well-being and to guaranteeing the plausibility of the clinical data. The IEC will report to the SC. The SC will discuss all the information and—if differences would be expected to have any bearing on the interventions and outcomes of the study—the study needs to be reassessed and the IEC will make recommendations regarding either re-evaluation of the extension of the recruitment period or the number of study centres, power calculation or termination of the trial.

Furthermore, the study centre will include a patient representative. To comply with current ethical regulations, the study will have an independent physician and a safety manager as well.

Since there are no unknown drugs or therapy are used in the study, no adverse or serious adverse events are expected. In the trial, IEC will examine safety variables after every 25 patients have completed. Investigators will report adverse or serious adverse events on a separate form which will be sent to the IEC. The SC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional and national ethical committee.

Data management

The SC members will perform the examinations listed in the section Data collection. Data will be handled by the SC. Manual data collection will be turned into a digital form by a study data manager. Insufficient data will be filtered when digitised from the paper. At the end of each examination, before releasing the patient, a data quality and validity check will be performed. Once the data have been digitised, another data check will be executed. The principal investigator (LS) will ensure that the digitalised data are accurate, complete and legible. Any missing, implausible or inconsistent recordings will be referred back to the investigator who performed the examinations. Patients with missing information will be asked via a phone call to fulfil the missing data. All changes will be documented. All data will be retained for 10 years.

Data confidentiality

Manually collected data will be stored safely in the corresponding centre (HOGYI) and only be accessible to the SC members. Digitisation will only take place under the supervision of the PI. When digitised, data are separated, tabulated and encrypted, and patient data are stored

securely. Digitised data will be anonymised as well (the patent's personal data will be coded and stored separately for identification). There are no other contractual agreements that limit such access for SC members. Other participants (study manager, IEC members) do not have access to the final trial dataset. The study protocol is free for public access.

Dissemination policy

Any changes or deviations in the study protocol will be updated on ClinicalTrials.gov. The changes will be reported to the research ethic committee as well.

Authorships will be implemented according to the International Committee of Medical Journal Editors recommendations.[34] Results will be submitted for publication in a peer-reviewed journal.

Centres

The study will start as a single-centre trial, but additional centres are planned to be involved in the future.

DISCUSSION

To our best 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. Although the progression of autonomic neuropathy is believed to be related to the duration of diabetes and poor metabolic status; animal studies have raised the question of whether changes in bladder function begin to occur soon after its onset.[35 36] Previous studies have suggested that DC is not the prime urodynamic finding in diabetics. Kaplan *et al*[37] found that detrusor overactivity was the most common finding. Kebapci *et al*[38] came to the conclusion that classic DC occurs in only 44% of adult women with type 2DM, followed for a mean of 13.85 years; more common findings are detrusor overactivity, stress and urge incontinence.

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 the urodynamic examinations before bothersome urinary symptoms are recognised 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.

Contributors ÁRM, PP, SK and LS conceptualised the protocol. ÁRM outlined the manuscript, while all the authors edited the manuscript. The statistical analysis plan was carried out by AZ. The final manuscript was reviewed and authorised by all of the authors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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