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ORIGINAL ARTICLE

Chronic kidney disease and urological disorders: systematic use of uroflowmetry in nephropathic patients

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ABSTRACT

Background. Chronic kidney disease (CKD) is a highly prevalent condition. Urologic disorders are known causes of CKD, but often remain undiagnosed and underestimated also for their insidious onset and slow progression. We aimed to evaluate the prevalence of urological unrecognized diseases in CKD patients by uroflowmetry.

Methods. We enrolled consecutive stable CKD outpatients. The patients carried out two questionnaires, the International Prostate Symptom Score and Incontinence Questionnaire-Short Form, and they also underwent uroflowmetry, evaluating max flow rate (Q_{max}), voiding time and voided volume values.

Results. A total of 83 patients (43 males, mean age of 59.8 ± 13.3 years) were enrolled. Our study showed 28 males and 10 females with a significant reduction of Q_{max} ($P < 0.001$) while 21 females reported a significant increase of Q_{max} ($P < 0.001$) with a prevalence of 49.5% of functional urological disease. Moreover, we showed a significant association between Q_{max} and creatinine ($P = 0.013$), estimated glomerular filtration rate ($P = 0.029$) and voiding volume ($P = 0.05$). We have not shown significant associations with age ($P = 0.215$), body mass index ($P = 0.793$), systolic blood pressure ($P = 0.642$) or diastolic blood pressure ($P = 0.305$). Moreover, Pearson's chi-squared test showed a significant association between Q_{max} altered with CKD ($\chi^2 = 1.885$, $P = 0.170$) and recurrent infection ($\chi^2 = 8.886$, $P = 0.012$), while we have not shown an association with proteinuria ($\chi^2 = 0.484$, $P = 0.785$), diabetes ($\chi^2 = 0.334$, $P = 0.563$) or hypertension ($\chi^2 = 1.885$, $P = 0.170$).

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Conclusions. We showed an elevated prevalence of urological diseases in nephropathic patients; therefore, we suggest to include uroflowmetry in CKD patient assessment, considering the non-invasiveness, repeatability and low cost of examination. Uroflowmetry could be used to identify previously unrecognized urological diseases, which may prevent the onset of CKD or progression to end-stage renal disease and reduce the costs of management.

Keywords: chronic kidney disease, end-stage renal disease, max flow rate, uroflowmetry, urological disorders

INTRODUCTION

The prevalence of chronic kidney disease (CKD) with various degrees of renal damage (stage 1/5 Kidney Disease Improving Global Outcomes (KDIGO) is increasing worldwide, being estimated 6–7.5% in Italy (CHARES study) and 13% in the world population [1]. Diabetes and hypertension are the most common causes of CKD, but other causes such as urological diseases have a prevalence that is not exactly known in adults [2]. These pathologies can be congenital or acquired. The most frequent are vesicoureteral reflux (VUR), which can determine the reflux nephropathy, recurrent urinary tract infections (UTIs), which may result in pyelonephritis, and urinary tract obstruction, which can be caused by anatomical and functional alterations [ureteropelvic junction syndrome, bladder neck stricture, congenital urethral valves, urethral stenosis, nephrolithiasis, malignancies and benign prostatic hyperplasia (BPH)], and the overactive bladder, especially in the females [3, 4]. These pathologies may present insidious onset and slow progression, which make them difficult to identify and define despite well-known complications. Hypertension, proteinuria, urine concentration defects, hyperkalaemia, metabolic acidosis, focal and segmental glomerulosclerosis and CKD are the most common complications that have a significant impact on long-term renal and cardiovascular prognosis [5, 6]. The aim of this study is to evaluate the prevalence of urological diseases in the nephrology department and their possible association with renal function, diabetes, hypertension, recurrent infection and proteinuria.

MATERIALS AND METHODS

The study protocol was approved by the Local Clinical Research Ethics Committee. The study conforms to the principles outlined in the Declaration of Helsinki and we obtained a written consent from each patient before enrolment.

Study design and subjects

We performed an observational, cross-sectional study on 83 clinically stable CKD outpatients, enrolled from January 2016 to December 2016, at the University Hospital 'Policlinico Umberto I' of Rome, Sapienza University of Rome, Italy. The study included patients with CKD on conservative therapy [estimated glomerular filtration rate (eGFR) $\leq$90 mL/min], Stage 1/5, and/or proteinuria, and/or hypertension and/or recurrent UTIs. Statins, antihypertensive, antiplatelet therapies and/or therapies with calcium, calcitriol and phosphate binders were continued in all patients included in the study. We recorded the anamnesis and excluded patients with urological or malformative pathologies and secondary nephropathies already known, severe infectious pathologies or malignancy in progress, patients with severe heart disease (Class IV New York Heart Association) or acute cardiac failure, degenerative neurological or psychiatric diseases, which did not allow the tests to be carried out properly, and acute coronary syndrome or stroke, within 3 months before the study. We did not enrol patients who refused to give consent or patients with missing data. The patients carried out two questionnaires, the International Prostate Symptom Score (I-PSS) [7, 8] and Incontinence Questionnaire-Short Form (ICIQ-SF) [9], and they also underwent uroflowmetry. eGFR was calculated with the abbreviated Modification of Diet in Renal Disease formula, expressed in mL/min/1.73 m^2 as defined by Levey *et al.* [10].

Anthropometric assessment

Body weight was determined to the nearest 0.1 kg using a calibrated digital scale. Body mass index (BMI) was calculated by the formula: [weight (kg)/height^2 (m^2)].

Blood pressure measurements

Blood pressure (BP) measurements were made in the dominant arm after 10 min of rest in the sitting position using a standard automatic sphygmomanometer and cuffs adapted to the arm circumference, according to the British Hypertension Society guidelines [11]. The mean of the three measurements was recorded for statistical analyses. The systolic BP (SBP) and diastolic BP (DBP) levels were taken as the points of appearance and disappearance of Korotkoff sounds, respectively. Hypertension was defined as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg on repeated measurements. We have also calculated ankle brachial pressure index, the measurement of the ratio of SBP in the ankle and in the arm (normal value 0.9–1).

Laboratory measurements

Blood was sampled the morning after overnight fasting of at least 12 h, for laboratory assessment. In all patients, the levels of fasting plasma glucose (mg/dL), haemoglobin (g/dL), total serum cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein (HDL) (mg/dL), creatinine (mg/dL), serum nitrogen (mg/dL), serum uric acid (mg/dL), calcium (mg/dL), phosphorus (mg/dL) and serum electrolytes (mEq/L) were measured using standard automated techniques. Low-density lipoprotein cholesterol (LDL) (mg/dL) was calculated using the Friedewald equation: LDL (mg/dL) = total cholesterol – HDL – (triglycerides/5). Urinalysis, urine culture and proteinuria 24 h (mg/24 h) was also carried out.

I-PSS

This questionnaire was developed by experts at the International Consultation on Prostatic Diseases, and it is universally accepted as an objective assessment tool for prostate enlargement (prostatic hypertrophy) in urinary disorders [7].

A symptom index for BPH was developed and validated by a multidisciplinary measurement committee of the American Urological Association (AUA). The final AUA symptom index includes seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying

and urgency. The AUA symptom index is clinically sensible, reliable, valid and responsive [8].

ICIQ-SF

The ICIQ-SF comprises three scored items and an unscored self-diagnostic item. It allows the assessment of the prevalence, frequency and perceived cause of urinary incontinence, and its impact on everyday life. The ICIQ is a brief and robust questionnaire that will be of use in outcomes and epidemiological research as well as routine clinical practice [9]. The normal value is <11.

Uroflowmetry

All patients carried out a uroflowmetry, with a commercially available instrument (Dantec Medical®, the Dan Flow 1100-WiFi version; Dantec Dynamics Ltd, a Nova Instruments Company, Garonor Way, Royal Portbury, Bristol, UK), evaluating max flow rate (Q_{max}) (20 < normal value < 35 mL/s), voiding time (normal value <20 s) and voided volume (normal value >150 mL) values [12].

Urodynamics is a tool of evaluating the pressure–flow relationship between the bladder and the urethra to assess the functional status of the lower urinary tract. The main goal of urodynamics is to aid in the correct diagnosis of lower urinary tract dysfunction based upon its pathophysiology [13]. Urodynamic studies should assess both the filling and storage phase as well as the voiding phase of bladder, and urethral function. Simple urodynamic tests involve performing non-invasive uroflow studies, obtaining post-void residual (PVR) urine measurements, the amount of residual urine in the bladder after a voluntary void and performing dual-channel cystometrography (CMG). Currently, the normal values of the PVR are poorly defined. However, most urologists agree that 50–100 mL volumes constitute the lower threshold defining abnormal residual urine volume [12]. CMG is the graphic recording of the pressure exerted at varying degrees of filling of the urinary bladder. It measures pressure generated by the bladder when voiding. A dual-channel CMG is used to assess the first sensation of filling, fullness and urinary urge. Bladder compliance and the evaluation of detrusor contractions can also be noted during this filling CMG [14].

Statistical analysis

Data management and analysis were performed using IBM® SPSS® Statistics 17 for Windows® software. The normality of variables was tested using the Kolmogorov–Smirnov method for normal distributions. All continuous variables were expressed as mean ± SD; categorical variables were expressed as number. Student's *t*-test or univariate analysis of variance was performed to determine differences between groups. Chi-squared test was used for comparison of categorical data. A probability value of $P < 0.05$ was considered to be statistically significant.

Ethical approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee at which the studies were conducted and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional Review Board approval has been obtained. Informed consent was obtained from all individual participants included in the study.

Table 1. Patients' characteristics

	Patients (n) = 83
Age (years)	57 ± 13
Voiding volume (mL)	360 ± 156
Voiding time (s)	36.7 ± 15.9
Max flow rate (mL/s)	26.0 ± 4.0
Creatinine (mg/dL)	0.96 ± 0.22
SBP (mmHg)	133 ± 17
DBP (mmHg)	81 ± 10
eGFR (mL/min/1.73 m^2)	81 ± 17
BMI (kg/m^2)	24.3 ± 2.1

Data are shown as mean ± SD.
BMI: Body Mass Index; DBP: Diastolic Blood Pressure; eGFR: estimated Glemerular Filtration Rate; SBP: Systolic Blood Pressure.

RESULTS

A total of 83 patients (43 males) with a mean age of 59.8 ± 13.3 were enrolled. Patient's characteristics are shown in Table 1. We have subdivided the sample according to the Q_{max}, voiding time and voiding volume [12] (Table 2).

A total of 24 patients with normal Q_{max} (20–35 mL/s) showed an eGFR of 81 ± 17 mL/min/1.73 m^2, while 59 patients with Q_{max} <20 mL/s showed an eGFR of 65 ± 25 mL/min/1.73 m^2 and 25 patients with Q_{max} >35 mL/s showed an eGFR of 66 ± 25 mL/min/1.73 m^2 ($P = 0.024$; Table 2).

The anamnestic information was collected, in the males, using I-PPS, with an average score of 12.4 (moderate symptomatology). In detail, 16.5% of the patients examined had a score <7 (mild symptomatology), while 50% and 33.5% of the patients showed I-PSS scores, respectively, indicative of a moderate and severe symptomatology. Moreover, 18 patients, males and females, with impaired Q_{max} presented a pathological ICIQ-SF with value >11, with a symptomatology that was irritative and obstructive. However, although the symptomatology was rather evident, only 22% had previously performed an urologic visit. We have found a high prevalence of 49.5% of urological disease in this study population. Also, we showed 28 males (66.6%) and 10 females (25.1%) with a significant reduction of Q_{max} ($P < 0.001$) and 21 females (52.7%) with a significant increase of Q_{max} ($P < 0.001$) with respect to the normal values. Moreover, we showed an association between pathological Q_{max} ($P < 0.001$) and voiding volume ($P = 0.05$) with an increase of creatinine ($P = 0.013$) and reduced eGFR ($P = 0.029$), while we did not show any significant associations with age ($P = 0.215$), BMI ($P = 0.793$), SBP ($P = 0.642$) and DBP ($P = 0.305$) (Table 2). Furthermore Pearson's chi-squared test showed a significant association between pathological Q_{max} with CKD ($\chi^2 = 8.495$, $P = 0.004$) (Figure 1) and recurrent infection ($\chi^2 = 8.579$, $P = 0.014$), while we did not show any association with proteinuria ($\chi^2 = 0.484$, $P = 0.785$), diabetes ($\chi^2 = 0.334$, $P = 0.563$) and hypertension ($\chi^2 = 1.885$, $P = 0.170$).

DISCUSSION

In this study, we showed a high prevalence of unrecognized urological disease in nephropathic patients (49.5%). In particular, in the female population, we reported mostly a high Q_{max}, with urgency urinary incontinence, indicating a possible overactive bladder, or bladder filling phase disease or pelvic floor dysfunction. Moreover, we showed a significant association between pathological Q_{max} and reduced eGFR, which could be

Table 2. One-way analysis of variance comparison between pathological Q_{max} (max flow rate <20 and >35 mL/s) and normal Q_{max} (max flow rate 20–35 mL/s) patient groups

Max flow rate	<20 mL/s	20–35 mL/s	>35 mL/s	
Patients (*n*)	34	24	25	P-value
Age (years)	63.0 ± 12.8	57.2 ± 13.4	57.7 ± 13.8	0.215
Voiding volume (mL)	273 ± 110	356 ± 155	334 ± 133	0.050
Voiding time (s)	39.7 ± 19.8	37 ± 16.5	32.1 ± 17.0	0.350
Creatinine (mg/dL)	1.3 ± 0.55	0.93 ± 0.22	1.1 ± 0.40	0.013
SBP (mmHg)	136 ± 19	136 ± 16	138 ± 15	0.642
DBP (mmHg)	80.7 ± 10.1	81.9± 11.1	80.7 ± 10.1	0.305
eGFR (mL/min/1.73 m^2)	65 ± 25	81 ± 17	66 ± 25	0.024
BMI (kg/m^2)	23.9 ± 2.5	23.8 ± 1.9	24.3 ± 1.8	0.793
Proteinuria (mg/24 h)	96.1 ± 78.2	65.8 ± 16.1	72.9 ± 55.6	0.125

Data are shown as mean ± SD.
BMI: Body Mass Index; DBP: Diastolic Blood Pressure; eGFR: estimated Glemerular Filtration Rate; SBP: Systolic Blood Pressure.

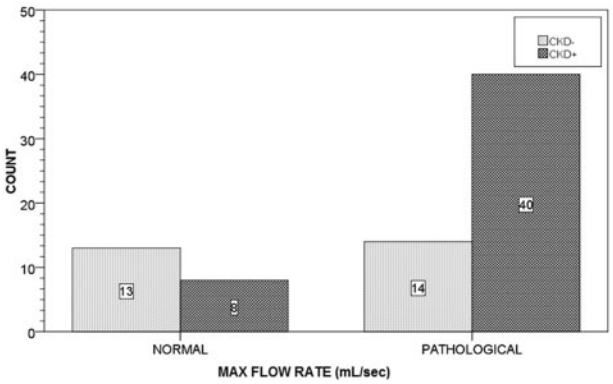

FIGURE 1: Boxes represent the frequencies. The number of CKD+ patients with pathological max flow rate was more than expected. Pearson chi-squared test shows that there is a statistically significant association between CKD+ and pathological max flow rate ($\chi^2 = 8.495$, $P = 0.004$). Normal, patients with max flow rate within the normal range; pathological, patients with max flow rate outside the normal range; CKD+, patients with chronic kidney disease; CKD−, patients without chronic kidney disease.

explained by increased intravesical pressure, especially in the overactive bladder or detrusor overactivity [15, 16]. Already in 1981, McGuire *et al.* [17] recognized the important role of high bladder pressure in myelodysplastic patients, and he identified in 40 cm H_2O the limit value of the bladder, below which no reflux occurred and only 10% of dilation happened, while for higher values 68% of patients presented VUR and 81% ureteral dilation. Indeed, increased intravesical pressure initially determines an increase in frequency and amplitude of ureteral contractions, and subsequently, reflux and/or dilation. These alterations remain reversible at an early stage, reducing the pressure with antimuscarinic drugs and intermittent catheterization, but afterwards ischaemic damage develops and detrusor muscle tissue becomes more rarefied and replaced by collagenous tissue, reducing detrusor contractility [18]. Furthermore, the fibrosis is irreversible and can thicken the bladder wall by narrowing the ureter resulting in ureterohydronephrosis. Gibbons [19] showed that high urinary tract pressures should be considered a determining factor in the pathophysiology of non-refluxing pyelonephritis, an insidious disease that may lead to irreversible renal lesions, without recovery in advanced stages. Therefore, early diagnosis and appropriate medical management could prevent possible damage to long-term kidney function [20, 21]. In our study, also patients with low Q_{max}, in particular males, showed a decreased eGFR, probably for the high incidence of bladder outlet obstruction (BOO) after 50 years. Hong *et al.* [22] evaluated the potential association between BPH and CKD in 2741 men presenting with lower urinary tract symptoms secondary to BPH of varying severity. Their results showed that only Q_{max} and PVR urine volume were identified as independent predictors of CKD, even if a decreased Q_{max}, with a history of hypertension and/or diabetes mellitus, were significantly associated with CKD. Also Cho *et al.* [23] showed that increased PVR was independently associated with a more rapid decline in renal function in patients with Type 2 diabetes. The pressure–flow relationship to diagnose obstruction is much better defined in men, though recently it is used in both genders. The causes of obstruction in women vary greatly, from anatomic as pelvic prolapse, pelvic masses and iatrogenic obstruction after stress incontinence, to functional as dysfunctional voiding and primary bladder neck obstruction [15]. Renal deterioration associated with chronic BOO is usually connected to impaired compliance and high-storage pressures [24]. Jhang *et al.* [25] evaluated the association between bladder function and CKD, showing that the bladder mucosa of these patients, especially in the advanced stage of CKD, presented a higher number of apoptosis cells and a lower expression of E-cadherin and tight junction of zonula occludens. The reduction of these two proteins has been associated with urothelial dysfunction, a barrier defect and an increase in intramucosal inflammation, which could justify a decrease in bladder capacity, an increased detrusor pressure and an increase in UTI. Therefore, not only could urological dysfunctions worsen renal function, but also CKD could favour urological alterations, in particular, bladder dysfunction [26]. In fact, in our study we showed significant associations between Q_{max} altered with CKD (Figure 1) and with recurrent infections. We also showed low demand for specialist urological visits, although the symptomatology, both irritative and obstructive, was rather evident, perhaps due to a lack of knowledge of urological expertise or to the belief that some urologic disorders are normally due to a physiological aging process. Low voided volumes need to be considered in the light of volume/Q_{max} nomogram position. Our study does not allow us to conclude if the urological abnormalities are the cause or consequence of CKD, but these diseases may be associated, and therefore it is useful to consider them in clinical practice [27].

Limitions

The limitations of our study are the relatively small, selective cohort of CKD outpatients and the cross-sectional, single-centre and observational design. Moreover, it is based on associations with surrogate endpoints; indeed, it demonstrated an 'association', rather than a 'causality' relationship, and therefore, the data should be considered as hypothesis-generating. The generated hypothesis hence needs further prospective follow-up studies with a larger number of patients and stronger endpoints to show causality. Moreover, we have selected consecutive patients with CKD, and/or proteinuria, and/or hypertension and/or recurrent UTIs, and this may have influenced the results. Another important limitation is that patients with advanced CKD are not included.

CONCLUSIONS

Uroflowmetry study could be used as a first-level test to identify possible urological disorders in nephropathic patients, especially considering the ease of execution, the repeatability, the non-invasiveness and the low cost. Multidisciplinary care in CKD patients could contribute to identify potential urological diseases associated with CKD, to improve the standard of care and clinical outcome.

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CONFLICT OF INTEREST STATEMENT

None declared.

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