

THE ASSOCIATION OF KIDNEY STRESS TEST WITH WATER SALT LOADING WITH ESTIMATED GLOMERULAR FILTRATION RATE DECLINE IN PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE 1-3

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ABSTRACT

Introduction. Kidney Disease Outcomes Quality Initiative (KDIGO) Group proposes the estimated glomerular filtration rate (eGFR) and albuminuria rate for a combined risk of clinical outcomes in patients with chronic kidney disease (CKD). However, the decline rate of eGFR can vary independently of the baseline eGFR.

The objective of the study was to improve the prognostic efficacy in chronic kidney disease (CKD) stage 1-3 due to new significant factors of CKD progression detected by renal stress test via the water-salt loading with 0.5 % sodium chloride solution, at a rate of 0.5% of the body weight.

Material and methods. In a single-centre prospective study, during 3-year follow-up period, from January 2016 to December 2018, 108 patients with CKD stage 1-3 (a, b) were examined. There were two groups: patients with rapidly progressive CKD whose

RÉSUMÉ

Test de stress rénal avec la charge d'eau salée et son association avec le déclin du débit de filtration glomérulaire estimé chez les patients avec de la maladie rénale chronique en stade 1-3

L'objectif de l'étude. Le groupe KDIGO propose le DFGe et l'albuminurie pour évaluer le risque combiné des résultats cliniques. Cependant, le déclin du DFGe peut varier indépendamment du DFGe de base. On a eu le but d'améliorer l'efficacité du pronostic chez les patients avec la maladie rénale chronique de stade 1-3 à l'aide de nouveaux facteurs pronostiques significatifs de la progression de la maladie rénale chronique détectés pendant le test de stress rénal via la charge d'eau salée avec une 0,5% solution de chlorure de sodium au taux de 0,5% du poids du corps.

Méthodes. Dans une étude prospective monocentrique, 108 patients atteints de maladie rénale

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eGFR throughout one-year follow-up decreased by 3 ml/min/1.73 m² and more (59 patients), and the group with a stable CKD, whose eGFR throughout one-year follow-up did not decrease or has decreased by less than 3 ml/min/1.73 m² (49 patients).

Results. No relationship between the renal functional reserve, stimulated GFR and a decline in eGFR throughout the year was found. The change in urine creatinine on the background of the water-salt loading was positively correlated with changes in eGFR throughout the year. Spearman's correlation coefficient was r_s 0.4 (p -0.02). The OR of decline in eGFR by more than 3 ml/min/1.73 m² throughout the year, with a decrease in urine creatinine level by more than 2 mmol/L, was 4.7 (95 % CI 1.9-12.0).

Conclusions. Improving the functionality of the renal stress test via the water-salt loading by measuring urine creatinine can help to identify the high-risk group for disease progression.

Keywords: chronic kidney disease, renal stress test, water-salt load, renal functional reserve.

List of abbreviations:

CKD – chronic kidney disease

RFR – renal functional reserve

eGFR – estimated glomerular filtration rate

INTRODUCTION

The prevalence of chronic kidney disease increases progressively with age, affecting about half of persons over 70 years old¹, because of the increase in the incidence of diabetes mellitus² and arterial hypertension³, as one of the determining factors in the development of end-stage chronic kidney disease (CKD).

The KDOQI (Kidney Disease Outcomes Quality Initiative) Guidelines identify the progression of kidney disease as a reduction of the renal function, assessed by determining the glomerular filtration rate (GFR), creatinine clearance or serum creatinine, in a patient who was examined with probable and comparative methods over time, or the onset of renal failure, which is determined by initiation of renal replacement therapy or by symptoms or complications of reduced renal function⁴.

Currently, according to the recommendations of the KDIGO Expert Group (Kidney Disease Improving Global Outcomes)⁵, the criteria for estimated glomerular filtration rate and the rate of albuminuria are used for a combined risk evaluation of renal consequences and other complications.

chronique de stade 1-3 (a, b) ont été examinés. Il y avait deux groupes : les patients atteints de la maladie rénale chronique progressive, dont le DFGe au cours du suivi a diminué de 3 ml/min/1,73 m² et plus (59 patients), et le groupe avec une maladie rénale chronique stable dont le DFGe au cours d'un an n'a pas diminué ou a diminué de moins de 3 ml/min/1,73 m² (49 patients).

Résultats. On n'a pas trouvé de relation entre la réserve fonctionnelle rénale, le DFGe stimulé et le déclin du DFGe dans un an. La variation de la créatinine urinaire pendant la charge d'eau salée était positivement corrélée aux variations du DFGe pendant un an (p 0,02). Le rapport de chances du déclin de DFGe de plus de 3 ml/min/1,73 m², en cas de diminution du taux de créatinine dans l'urine de plus de 2 mmol/L, est 4,7 (IC 95%: 1,9-12,0).

Conclusions. L'amélioration du test de stress rénal via la charge de l'eau salée avec l'évaluation de la créatinine dans l'urine peut aider à identifier le groupe à haut risque de progression de la maladie rénale chronique.

Mots-clés: la maladie rénale chronique, la progression, le test de stress rénal, la charge d'eau salée, la réserve fonctionnelle rénale

Abréviations: MRC – la maladie rénale chronique, RFR – la réserve fonctionnelle rénale, DFGe- le débit de filtration glomérulaire estimé.

However, the decline rate of eGFR among patients can vary independently of the baseline eGFR⁶. This explains why patients with the same initial stage of CKD may have different course and clinical consequences. Some of them have had stable values of the estimated glomerular filtration rate (eGFR) for several years. This condition can be called stable CKD. In few patients, eGFR increases; it is the so-called reversible CKD. In the majority of patients, however, eGFR decreases over time; that is the progressive CKD⁷.

A decline in eGFR may serve as an adequate indicator to evaluate the disease severity⁸ and a tool to monitor the adequacy of treatment. The decline rate of eGFR level is an independent predictor of end-stage CKD, which will require renal replacement therapy⁹ and mortality¹⁰.

A rapid decline in eGFR is determined by a loss of 3 ml/min/1.73 m² of glomerular filtration throughout the year, which is a threefold average annual decline rate of GFR associated with ageing. It is associated with an increased risk of both cardiovascular and overall mortality¹¹.

Patients, whose eGFR declines by more than 3 ml/min/1.73 m² throughout the year, require intensive reno-protective therapy.

Currently, in addition to determining the glomerular filtration rate, the renal functional reserve, which reflects the ability of the kidneys to increase glomerular filtration in response to stimulating factors, is used to assess the functional state of the kidneys¹². In medical practice, various methods of determining the renal functional reserve are used. However, the prognostic value of the renal functional reserve in patients with chronic kidney disease has not been fully clarified yet. According to the available study findings, the conclusions are contradictory. Some studies indicate that, with the preserved renal functional reserve, it progressively decreases with the progression of CKD¹³ but can be maintained even at the glomerular filtration rate of 15 ml/min¹⁴. Renal functional reserve (RFR) is preserved for at least 90 years, both in men and in women¹⁵. It is also paradoxical that the renal functional reserve may be absent in patients with preserved or slightly reduced renal function, and vice versa, may be high in patients with low baseline glomerular filtration rate. The preoperative renal reserve determined by dopamine in living donors is associated with a short-term prognosis of kidney function – glomerular filtration rate 3 months after donation, but it does not show an association with the glomerular filtration rate after 5 years¹⁶.

THE OBJECTIVE OF THE STUDY was to improve the efficacy of the prognosis of patients with CKD: to determine the relationship between RFR and the decline in eGFR throughout one-year follow-up, to detect additional prognostically significant factors of CKD progression in determining renal functional reserve via the water-salt loading test with 0.5 % sodium chloride solution at the rate of 0.5 % of the body weight.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine. The study involved patients over 18 years of age with clinical and laboratory data, which allowed to establish the diagnosis of CKD according to the KDIGO 2012 *Clinical Practice Guidelines* for the evaluation and management of chronic kidney disease of Stage 1-3 (a and b) (decline in GFR to 30 ml/min/1.73 m²). Exclusion criteria were patient unwillingness to participate in the study, Stage 4-5 of CKD, pregnancy and active onco-pathology. All patients gave their informed consent to participate in the study.

In a single-centre prospective study, during 3-year follow-up period, from January 2016 to December 2018, 108 patients with CKD of Stage 1-3 (a, b) were examined on the basis of the Municipal Institution of the Kyiv Regional Council „Kyiv Regional Hospital No. 2“.

Patients were examined using the standard methods for determination of anthropometric measures, the calculated values of body area and body mass index. The blood pressure was measured. Renal functional reserve was determined using the water-salt loading test with 0.5 % sodium chloride solution at the rate of 0.5 % of the body weight^{17,18}. The examination was performed on an outpatient basis in the morning on an empty stomach after a 12-hour fast.

Venous blood was collected to determine serum creatinine concentration. Serum creatinine was used to calculate the baseline glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. The patient emptied the bladder. A urine sample was used to determine the urine creatinine concentration. Then, the patient in the presence of a doctor took orally 0.5 % sodium chloride solution at the rate of 0.5 % of the body weight for 5-7 minutes and was at rest in a sitting position for one hour. After one hour, venous blood was collected again to determine serum creatinine concentration and urinary bladder emptying. The volume of urine obtained in induced diuresis and the creatinine concentration in it were determined.

According to the formula, creatinine excretion per one hour is calculated:

$$CE = U_c \cdot D60,$$

where CE is creatinine excretion; U_c is the creatinine concentration in the urine portion of induced diuresis collected within 1 hour, expressed in mmol/L; D60 is the amount of urine collected within 1 hour.

Based on creatinine excretion and the serum creatinine level determined one hour after loading with 0.5 % sodium chloride solution, GFR was calculated based on creatinine clearance:

$$CC = CE/60/P_c,$$

where P_c is plasma creatinine concentration.

To calculate a standardized body surface area of 1.73 m² using the Dubois and Dubois formula, the patient's body surface area (BSA) is calculated on the basis of patient's height and body mass:

$$BSA = 0.007184 \times (\text{height in cm})^{0.725} \times (\text{mass in kg})^{0.425}$$

Note: The calculations were performed using an online calculator.

Stimulated eGFR is calculated based on creatinine clearance and the actual body surface area:

$$eGFR_{st} = U_c/BSA \cdot 1.73$$

Table 1. Clinical characteristics of patients with CKD stage 1-3 at baseline

| Parameter | All examined patients | Men | Women |
|--|-----------------------|---------------------|---------------------|
| Height, cm | 169.3±9.2 | 175.6±7.6* | 163.8±5.8* |
| Mass, kg | 84.5±12.7 | 88.2±13.1* | 80.9±11.5* |
| BMI, kg/m ² | 29.4±4.0 | 28.5±3.5* | 30.2±4.4* |
| Waist line, cm | 104 (98;110) | 104 (98;110) | 104 (96;110) |
| Systolic blood pressure, mm Hg | 150 (130;160) | 150 (135;160) | 140 (130;165) |
| Diastolic blood pressure, mm Hg | 90 (80;100) | 90 (80;100) | 90 (80;90) |
| Serum creatinine, μmol/L | 103.5 (83.5;122.8) | 114.7 (100.5;152.5) | 90.1 (71.2;107.2) |
| eGFR, ml/min/1.73 m ² | 60.4±19.9 | 58.8±21.4* | 62.1±18.5* |
| Serum uric acid, μmol/L | 316.8±88.9 | 312.0±81.7 | 321.6±96.9 |
| RFR, % | 74.1 (4.7;128.8) | 88.8 (38.7; 152.3) | 72.9 (-13.2; 111.2) |
| Change in eGFR throughout a year, ml/min/1.73 m ² | -5.6±10.4 | -7.3±9.7 | -3.9±11.1 |

Renal functional reserve is determined by the percentage ratio between stimulated glomerular filtration rate and the baseline glomerular filtration rate:

$$\text{RFR} = (\text{eGFR}_{\text{st}} - \text{eGFR}_{\text{b}}) / \text{eGFR}_{\text{b}} \cdot 100 \%$$

In addition, changes in the urine creatinine concentration of spontaneous and induced diuresis were evaluated. Re-examination of patients with determining eGFR was performed in a year. The dynamics of eGFR value throughout the year was evaluated.

Statistical processing of information was carried out using StatSoft Statistica v6.0. and SPSS Statistics 17.0. The mean (M) and standard deviations (SD) were used to evaluate data with a normal distribution; the median value (Me) and quartile range were used to evaluate data with an abnormal distribution (25; 75). To compare unrelated data according to quantitative criterion, nonparametric statistical criteria were used, in particular, the Mann-Whitney U-test for data with an abnormal distribution and the Student's *t*-test for data with a normal distribution. To compare paired values, the Student's *t*-test and the Wilcoxon signed-rank test for normal and abnormal distribution were used, respectively. The relationship between parameters was established using a nonparametric measure of rank correlation – the Spearman's correlation coefficient. The results were considered statistically significant with $p < 0.05$. Using tables 2×2, the change in urine creatinine level associated with the progressive CKD was determined.

Patients aged 29-78 years participated in the study; an average age was 63 years (58; 70). There were 54 men (50 %) and 54 women (50%). According to the disease stage, the distribution was as follows: Stage 1 was diagnosed in 8 patients (7 %), Stage 2 in 46 patients (43 %), Stage 3 in 54 patients (50 %). The main characteristics of the examined patients are shown in Table 1.

RESULTS

The analysis revealed no relationship between the renal functional reserve, stimulated GFR, serum uric acid, urine creatinine concentration in induced diuresis and a decline in eGFR throughout the year. The change in urine creatinine on the background of the water-salt loading was positively correlated with changes in eGFR throughout the year. Spearman's correlation coefficient was $r_s 0.4$ ($p=0.02$). An increase in urine creatinine concentration of induced diuresis in relation to urine creatinine concentration of morning spontaneous diuresis was observed in 30 patients (28 %) on the background of water-salt loading. A decrease in urine creatinine concentration was observed after the test in 78 patients (72%).

To evaluate the effect of this risk factor on the decline in eGFR, the patients were divided into 2 groups: patients with rapidly progressive CKD whose eGFR throughout one-year follow-up decreased by 3 ml/min/1.73 m² and more, and the group with a stable CKD whose eGFR throughout one-year follow-up did not decrease or has decreased by less than 3 ml/min/1.73 m². The group with progressive CKD included 59 patients and 49 patients in the group with stable CKD. Their main characteristics are shown in Table 2. The patients of both groups are comparable according to the main anthropometric measures (Table 2). They have metabolic disorders, as evidenced by an increase in waistline and body mass index. Significantly higher values of BMI were observed in the stable CKD group compared with the group where eGFR decreased by more than 3 ml/min/1.73 m² throughout the year.

In both groups, there were no differences in baseline blood pressure, serum creatinine before and after the water-salt loading test, baseline and stimulated eGFR, the state of RFR (Table 3).

Table 2. Anthropometric measures of patients with stable and progressive CKD.

| Parameter | Progressive CKD, n=59 | Stable CKD, n=49 | p-level |
|------------------------|-----------------------|-------------------|---------|
| Men | 32 | 22 | |
| Women | 27 | 27 | |
| Age, years | 66.5 (58;74) | 62 (59;70) | 0.456 |
| Height, cm | 170.0±7.9 | 167.5±8.2 | 0.691 |
| Mass, kg | 83.4±12.5 | 88.4±8.9 | 0.395 |
| BMI, kg/m ² | 28.8±3.8 | 31.5±3.8 | 0.038 |
| Waist line, cm | 104.5 (98;110) | 108 (101.5;110.5) | 0.606 |

Table 3. The results of the water-salt loading test to determine RFR and the values of patients after one year.

| Parameter | Progressive CKD, n=59 | Stable CKD, n=49 | p-level |
|---|-----------------------|---------------------|---------|
| Systolic blood pressure, mm Hg | 150 (140;160) | 150 (140;167.5) | 0.500 |
| Diastolic blood pressure, mm Hg | 90 (80;100) | 90 (80;100) | 0.677 |
| Serum creatinine before the test, μmol/L | 109.8 (91.9;121.6) | 101.0 (71.9;144.5) | 0.692 |
| Serum creatinine an hour after the water-salt loading test, μmol/L | 110.2 (91.9; 129.3) | 102.0 (72.3; 144.6) | 0.640 |
| Baseline eGFR ml/min/1.73 m ² | 55.8±15.2 | 58.8±21.3 | 0.821 |
| Stimulated eGFR after the water-salt loading test, ml/min/1.73 m ² | 108.3 (67.6;119.9) | 96.1 (37.7; 144.7) | 0.636 |
| RFR, % | 87.4 (37.1; 120.1) | 59.9 (-21.7;121.3) | 0.444 |
| Urine creatinine in spontaneous diuresis, mmol/L | 10.5 (7.9; 11.5) | 7.6 (4.8; 9.9) | 0.056 |
| Urine creatinine in induced diuresis, mmol/L | 7.2 (4.9; 9.4) | 7.0 (5.3; 9.2) | 0.747 |
| Change in the urine creatinine concentration during the loading, mmol/L | -2.05±2.5 | -0.18±2.1 | 0.019 |
| eGFR after a year, ml/min/1.73 m ² | 43.4±15.2 | 61.1±25.1 | 0.009 |
| Change in eGFR throughout a year, ml/min/1.73 m ² | -12.4±8.3 | 2.4±5.7 | <0.0001 |

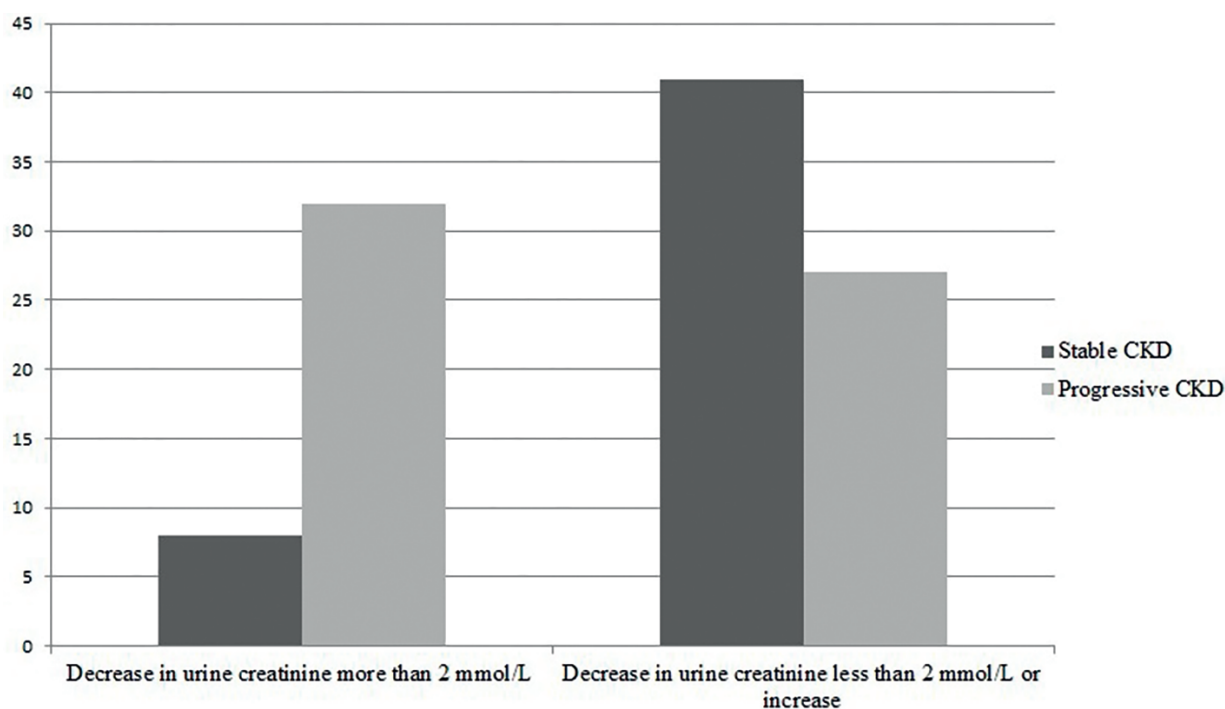


Figure 1. The ratio of patients depending on the change in urine creatinine concentration and the course of CKD.

Patients with progressive CKD had significantly lower values of eGFR after one-year follow-up (p-level < 0.0001). Urine creatinine concentration decreased on the background of the water-salt loading (p-level 0.002). In patients with stable CKD, the values of eGFR did not statistically differ at the beginning of the study and after one-year follow-up, and there was no significant difference between the spontaneous creatinine concentration and induced diuresis on the background of the water-salt loading test. Using the odds ratio (OR), we revealed the change in urine creatinine level which is associated with the risk of decline in eGFR by more than 3 ml/min/1.73 m² throughout the year (Figure 1): OR with a decrease in urine creatinine level by more than 2 mmol/L was 4.7 (95 % CI 1.9-12.0).

DISCUSSION

No studies on the relationship between the state of RFR and decline in eGFR have been found. The findings suggest that the ability of the kidney to respond to stressful factors by increasing glomerular filtration is not decisive in maintaining eGFR throughout the year. This is due to the fact that available findings of both the historical and relatively recent studies show that, over time, the role of the main effector in the progression of CKD has passed from the glomeruli, which are responsible for the increase in GFR in response to provoking stimuli, to the interstice. However, the state of the renal functional reserve should be taken into account for the individualization of reno-protection strategy^{19,21}. At the same time, the prognostic value of the change in urine creatinine concentration, before and after the water-salt loading test with 0.5 % sodium chloride solution at a rate of 0.5% of body weight, was revealed. The ability of the kidney to maintain or increase the urine creatinine concentration under the influence of the stress factor is associated with a stable course of CKD when eGFR decreases by less than 3 ml/min/1.73 m² throughout the year.

CONCLUSIONS

With improving the functionality of the test to determine the renal functional reserve as a routine method of examination of nephrology patients, it is possible to individualize the prognosis of a particular patient according to the progression of chronic kidney disease, to identify the high risk group for disease progression and to intensify therapy and monitoring of kidney function by determining the change in the urine creatinine concentration.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study“

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