Research article/Raziskovalni prispevek

SERUM CYSTATIN C – A NEW MARKER OF GLOMERULAR FILTRATION RATE

SERUMSKI CISTATIN C – NOV OZNAČEVALEC GLOMERULNE FILTRACIJE

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Key words: *glomerular filtration rate; renal disease; serum cystatin C; serum creatinine; CrEDTA clearance*

Abstract – Background. *Estimation of the glomerular filtration rate is an essential part of the evaluation of patients with renal disease. A standard for glomerular filtration rate assessment is CrEDTA clearance. Serum creatinine is the most commonly used marker to estimate the glomerular filtration rate, but it is often not enough accurate. Recently serum cystatin C has been proposed as a new endogenous marker of glomerular filtration rate.*

Patients and methods. *A total of 231 patients (100 woman and 131 men), who performed CrEDTA clearance in previous 17 months, were enrolled in our study. In each patient serum creatinine and serum cystatin C were also determined. Average age of our patients was 55 years (from 7 to 85 years).*

Results. *Average CrEDTA clearance was 54.4 ml/min/1.73 m² (from 2 to 186 ml/min/1.73 m²). Average serum creatinine concentration was 270.2 µmol/l (from 64 to 915 µmol/l) and average serum cystatin C concentration was 2.53 mg/l (from 0.59 to 6.99 mg/l). The correlations between CrEDTA clearance, serum creatinine and serum cystatin C were statistically significant. The correlation between CrEDTA clearance and serum cystatin C was better than correlation between CrEDTA clearance and serum creatinine.*

Conclusions. *CrEDTA clearance, serum creatinine and serum cystatin C are comparable markers of renal function. Based on our study, serum cystatin C is a more reliable measure of glomerular filtration rate than serum creatinine.*

Ključne besede: *glomerulna filtracija; ledvična bolezen; serumski cistatin C; serumski kreatinin; CrEDTA očistek*

Izvleček – Izhodišča. *Ocena glomerulne filtracije (GF) je pomemben del obravnave bolnika z ledvično boleznijo. GF ali njena sprememba je lahko prvi znak ledvične bolezni, lahko kaže na resnost ledvične bolezni, omogoča spremljanje poteka ledvične bolezni in pomaga pri določanju pravilnega odmerka zdravil, ki se izločajo preko ledvic. Temeljna metoda za oceno GF je očistek snovi. To je prostornina plazme, ki se v določeni časovni enoti očisti te snovi z izločanjem v seč. GF bi lahko natančno določili s pomočjo snovi, ki v telesu nastaja stalno, ki se izloča iz telesa izključno s prosto filtracijo, ki se v ledvicah ne presnavlja in ne sintetizira in ki se v ledvičnih tubulih ne secernira in ne reabsorbira. Zaenkrat ni poznana endogena snov, ki bi zadostila vsem tem pogojem. V vsakdanji klinični praksi se za oceno GF najpogosteje uporablja serumska koncentracija kreatinina, ki pa pogosto ni dovolj natančna. Očistek kreatinina je boljši pokazatelj GF kot serumska koncentracija kreatinina, vendar zahteva 24-urno zbiranje urina, ki pogosto ni zanesljivo. Standardna referenčna metoda za določanje GF je očistek CrEDTA, vendar je to radioizotopni označevalec, zato ga ni možno zelo pogosto uporabiti pri istem bolniku. V zadnjem času se kot eden novih označevalcev glomerulne filtracije pojavlja serumska koncentracija cistatina C. Cistatin C je inhibitor proteaz, v telesu nastaja stalno v vseh jedrnih celicah in se prosto filtrira čez glomerulno membrano. Velik del se ga katabolizira v proksimalnem tubulu, vendar se ne secernira niti se ne vrača v krvni obtok. Zaradi razgradnje v proksimalnem tubulu se njegov očistek ne da meriti, njegova serumska koncentracija pa je dober pokazatelj GF. Pomen cistatina C za oceno GF je sicer poznan že mnogo let, se pa v preteklosti ni uporabljal, saj je bilo njegovo določanje tehnično zelo težavno.*

Bolniki in metode. *V raziskavi je sodelovalo 231 bolnikov (100 žensk in 131 moških), ki so imeli v obdobju 17 mesecev določen očistek CrEDTA. Povprečna starost bolnikov je bila 55 let (od 7 do 85 let). Sočasno smo pri vseh v raziskavo vključenih bolnikih izmerili še serumsko koncentracijo kreatinina in serumsko koncentracijo cistatina C. Kreatinin v serumu smo določili s kinetično metodo po Jaffeju brez deproteinizacije (Roche Diagnostics), serumski cistatin C pa z nefelometrično metodo s pomočjo trdih nosilcev (Dade Behring). Pri merjenju očistka CrEDTA smo uporabili metodo enkratnega bolu-*

sa označevalca CrEDTA. Njegov odmerek smo določili matematično na podlagi telesne teže in višine.

Rezultati. *Povprečna vrednost očistka CrEDTA je bila 54,4 ml/min/1,73 m² (2 do 186 ml/min/1,73 m²). Povprečna vrednost serumske koncentracije kreatinina v raziskavi zajetih bolnikov je bila 270,2 µmol/l (64 do 915 µmol/l). Povprečna vrednost serumske konentracije cistatina C je bila 2,53 mg/l (0,59 do 6,99 mg/l). Ugotovili smo statistično pomembno korelacijo med očistkom CrEDTA, serumsko koncentracijo kreatinina in serumsko koncentracijo cistatina C. Korelacija je bila boljša med očistkom CrEDTA in serumsko koncentracijo cistatina C (r = –0,792) kot pa med očistkom CrEDTA in plazemsko koncentracijo kreatinina (r = –0,702). Boljšo korelacijo smo ugotovili tudi med očistkom CrEDTA in recipročnimi vrednostmi cistatina C (r = 0,895) kot pa med očistkom CrEDTA in recipročnimi vrednostmi serumske koncentracije kreatinina (r = 0,873).*

Zaključki. *V naši raziskavi smo potrdili, da je serumska koncentracija cistatina C dober pokazatelj glomerulne filtracije. Ugotovili smo boljšo povezanost med očistkom CrEDTA in serumskimi koncentracijami cistatina C v primerjavi s serumskimi koncentracijami kreatinina. Rezultati naše raziskave potrjujejo rezultate večine raziskav, ki kažejo, da je serumska koncentracija cistatina C boljši pokazatelj GF od serumske koncentracije kreatinina. Pa tudi v raziskavah, kjer niso potrdili, da je serumska koncentracija cistatina C boljši pokazatelj GF kot serumska koncentracija kreatinina, so ugotovili, da je bila GF ocenjena s pomočjo serumskega cistatina C primerljiva z oceno GF, ugotovljeno s serumsko koncentracijo kreatinina in z očistkom kreatinina. V klinični praksi ima določanje cistatina C prednost pred določanjem kreatinina predvsem pri otrocih in starostnikih, pri bolnikih z začetno ledvično odpovedjo in pri bolnikih, pri katerih je potrebno pogosto in natančno določanje GF, kot tudi pri bolnikih po presaditvi ledvic.*

Introduction

Glomerular filtration takes part in 1.6 to 2.4 million glomeruls. It is determined by filtration pressure and hydraulic permeability of glomerular basal membrane (filtration coefficient). Estimation of glomerular filtration rate (GFR) is important part of the evaluation of the patient with renal disease. Glomerular filtration is a sum of filtrations in each nephron, and therefore an indicator of the functioning glomerular mass (1).

Estimation of GFR is important, because (1):

- It can be the first and the only clinical sign of the renal disease (e. g. loss of functioning nephrons cause decrease of GFR, as urine tests are normal and balance of water and electrolytes is still preserved);
- It can be used for estimation of the severity of renal disease and its follow-up (e. g. decrease of GFR may be the sign of progression of the underlying renal disease or its deterioration from other potentially reversible causes);
- It helps to determine adequate administration of drugs, excreted through the kidneys by glomerular filtration (e.g. if the GFR is decreased, excretion of the drug is decreased and causes increase of the concentration of the drug in the plasma, therefore, adjustment of administration is needed).

Basic method for the estimation of GFR is renal clearance. It is defined as the volume of plasma that can be completely cleared of a particular substance into urine within certain unite of time (2). GFR could be accurately defined by the substance which is continuously produced in the body and exclusively excreted by free filtration, not being metabolically processed, synthesized nor secreted and reabsorbed in renal tubules (3). An endogenous substance to satisfy all these conditions has not been found yet. Thus, there are different methods for estimation of GFR, and each of them has its advantages and disadvantages.

In clinical practice serum creatinine concentration is the most commonly used marker to estimate GFR, but it is often not accurate enough (4). Standard referential method for GFR assessment is CrEDTA clearance, but as it is a radiolabelled marker and some radiation is administered to patient, it cannot be used very often in the same patient. As some diseases demand more often to estimate GFR, serum cystatin C concentration is possible alternative. Cystatin C has been known for many years as a marker of GFR. However, it had not been used in the past because of its technically demanding application (1, 5).

The aim of our research was to find out if serum cystatin C concentration is a good marker of GFR and if it can be compared with CrEDTA clearance. We also aimed to find out if cystatin C could be a better indicator of GFR than serum creatinine concentration.

Patients and methods

There were 231 patients included in our study, 131 were male (56.7%) and 100 female (43.3%). Patients' average age was 55.5 years, ranged from 7 to 85 years. Their average weight

was 76.8 kg (ranged from 23 to 119 kg) and their average height was 169.2 cm, ranged from 125 to 194 cm.
In all patients included in the study CrEDTA clearance was estimated in the period from November 2001 till the begging of April 2003. At the same time as CrEDTA clearance was estimated, serum creatinine and serum cystatin C were measured. Serum creatinine was measured by the kinetic method according to Jaffe without deproteinisation (Roche Diagnostics), serum cystatin C was measured by particle-enhanced immunonephelometric method (Dade Behring). CrEDTA clearance was determined by single bolus method. Clearance was calculated mathematically on the basis of body weight and height. Blood samples were taken four times, first before the administration of the radiolabelled marker, and later 120, 180 and 240 minutes after parenteral application of the marker. On the basis of the measurement of the gamma radiation CrEDTA clearance was calculated in ml/min/1.73 m^3.
In statistical analysis SPSS for Windows and MedCalc were used. Mean values, range and standard deviation (SD) were calculated. Pearson's correlation coefficient was used for finding out correlation between CrEDTA clearance and serum creatinine and cystatin C, as well as correlation between CrEDTA clearance and reciprocal values of serum creatinine and cystatin C.

Results

Average CrEDTA clearance in our patients was 54.4 ml/min/1.73 m^2, ranged from 2 to 186 ml/min/1.73 m^3 (SD ± 41.06). Serum creatinine concentration values were from 64 to 915 µmol/l, average value was 270.2 µmol/l (SD ± 214.2). Serum cystatin C concentration values were from 0.59 to 6.99 mg/l, average value was 2.53 mg/l (SD ± 1.62). There were no statistically significant differences between genders considering the values of CrEDTA clearance, serum creatinine concentration and cystatin C. Statistically significant correlation was found between CrEDTA clearance, serum creatinine and serum cystatin C. Correlation was better between CrEDTA clearance and serum cystatin C (r = –0.792) than between CrEDTA clearance and serum creatinine (r = –0.702) (Table 1, Figures 1, 2). These two correlation coefficients differ significantly (P = 0.028). Also, reciprocal values of serum cystatin C correlated better with CrEDTA clearance than reciprocal values of the serum creatinine (Table 1, Figures 3 and 4).

Table 1. *Correlations between CrEDTA clearance, serum creatinine, serum cystatin C and 1/creatinine and 1/cystatin C.*

Razpr. 1. *Korelacija med CrEDTA očistkom in serumskimi koncentracijami kreatinina in cistatina C ter recipročnimi vrednostmi kreatinina in cistatina C.*

	CrEDTA clearance (ml/min/1.73 m^2) CrEDTA očistek (ml/min/1,73 m^2)	P <
Creatinine (µmol/l) Kreatinin (µmol/l)	r = – 0.702	0.001
1/creatinine 1/kreatinin	r = + 0.873	0.001
Cystatin C (mg/l) Cistatin C (mg/l)	r = – 0.792	0.001
1/cystatin C 1/cistatin C	r = + 0.895	0.001

r = Pearson' correlation coeficient
r = Pearsonov koeficient korelacije

Discussion

GFR or its changed value can be the first sign of renal disease and also an indicator of severity of the renal disease. It

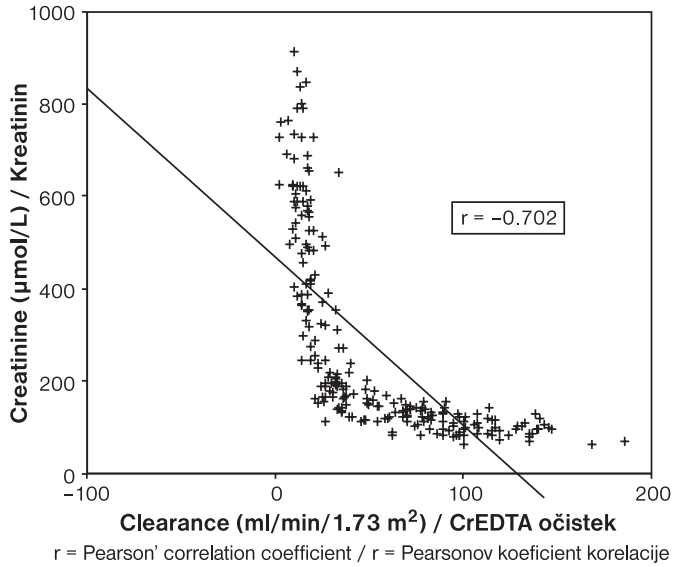

Figure 1. *Correlation between CrEDTA clearance and serum creatinine.*

Sl. 1. *Povezava med CrEDTA očistkom in serumskim kreatininom.*

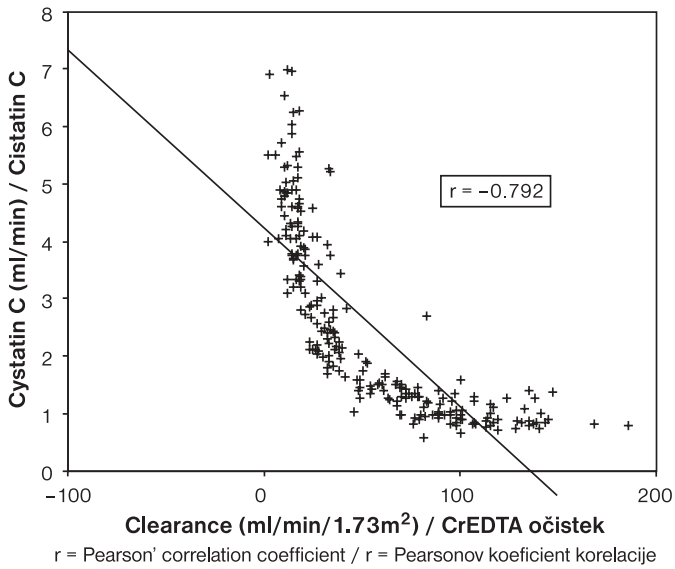

Figure 2. *Correlation between CrEDTA clearance and serum cystatin C.*

Sl. 2. *Povezava med CrEDTA očistkom in serumskim cistatinom C.*

enables us to follow-up the course of the renal disease and help us to administer the drugs, excreted through kidneys. There are different methods for estimation of GFR, each of them with their advantages and disadvantages. In many European countries standard method for estimation of GFR is CrEDTA clearance. It is a radiolabelled marker enabling accurate renal clearance with less than one per cent differences between measurements, in spite of small amount of substance used. Method of CrEDTA clearance with single bolus of CrEDTA is comparable with inulin clearance, which is the golden standard for GFR measurement (6). CrEDTA marker has one month splitting time, what makes it economical and convenient for storage. Its disadvantage is radiation and

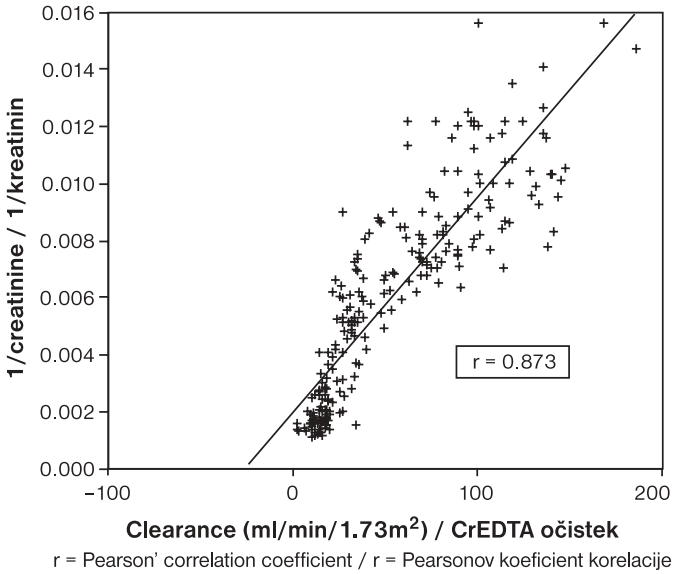

Figure 3. *Correlation between CrEDTA clearance and 1/serum creatinine.*

Sl. 3. *Povezava med CrEDTA očistkom in 1/kreatininom.*

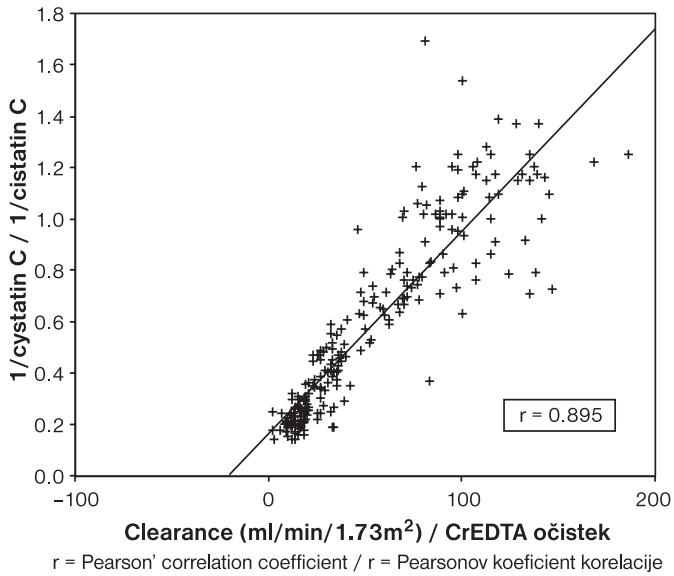

Figure 4. *Correlation between CrEDTA clearance and 1/serum cystatine C.*

Sl. 4. *Povezava med CrEDTA očistkom in 1/serumskim cistatinom C.*

almost always higher price in comparison with other markers. CrEDTA clearance was also used in our research as standard for estimation of GFR.

Serum creatinine is the most often used method for GFR estimation in clinical practice. Creatinine is released relatively steadily from muscle tissue, its concentration in the serum changes daily for less than 10%. Creatinine is freely filtered, it is not reabsorbed nor metabolized in kidneys, but partially secreted into proximal tubule. Tubular secretion causes increase of creatinine clearance for 10–20% (7). As plasma concentration increase, tubular secretion of creatinine increases, leading to an overstimation of GFR in patients with moderate to severe decreases of GFR (8). Serum creatinine concentration depends on muscle mass and food intake (meat in diet). Another disadvantage is that creatinine is usually measured by the Jaffe reaction, based on cromogen reaction. According to this method, other non-creatinine cromogens are present in plasma, which cannot be find in urine. Thus creatinine concentration is overestimated in plasma and the calculated clearance is underestimated (for 10 to 20%). At normal kidney function, both irregularities are annulled, so that creatinine clearance is very close to the inuline clearance. At the very beginning of the renal disease, tubule secretion increases and causes false increase of GFR (10–20). A number of drugs used in clinical practice affect this tubular secretion of creatinine and thus may rise the plasma creatinine and reduce the calculated creatinine clearance (e.g. trimethoprim, cimetidine ...). Creatinine clearance gives a better estimate of GFR than does serum creatinine concentration, but it requires inconvenient urine collections (13). Despite all disadvantages, serum creatinine concentration is used for GFR estimation as it is simple and cheap.

Because of all mentioned facts, there is a need for a new marker of GFR, which can be easily measured and which would not depend on age, gender, weight, height, food intake and without possibility to be influenced by the concentration of other substances in the serum. Recently, cystatin C has been proven as one of such markers. It is protease inhibitor, produced by nucleated cells at a constant rate and is freely filtered through glomerular membrane (14). Great part is catabolised in proximal tubule, but it is not secreted, not returned into blood flow. This latter property negates calculation of cystatin C clearance using urine concentrations of cystatin C, but its serum concentration is a good marker of GFR. Its concentration cannot be affected by inflammation, fever and/or outside agents (14, 15). There are contradictory data considering possible influence of malignant diseases on the serum concentration of cystatin C, however, most authors deal opinion that malignant processes do not influence on serum cystatin C concentration (14–18). Advantage of cystatin C is also that its referential values do not differ in children and adults, they do not depend on gender, age or muscle mass (19, 20).

There have been some studies published on the role of cystatin C in estimation of GFR. Their results show that cystatin C serum concentration is better indicator of GFR than creatinine serum concentration (21, 22), especially in patients with spine injury (26), patients with liver cirrhosis (31) and patients with diabetes (32). Results of our study confirm good correlation of cystatin C concentration and CrEDTA clearance. Findings show that serum cystatin C is better marker of GFR than creatinine. However, some studies have not confirmed cystatin C serum concentration as better indicator of GFR than serum creatinine concentration (35–38). Even in these studies, GFR estimated by cystatin C serum is comparable with the estimation of GFR by serum creatinine concentration and creatinine clearance (33, 34).

Considering known facts, in clinical practice, cystatin C as marker of GFR has advantage in usage in children and elderly, patients with incipient renal failure, patients after kidney transplantation and those who need more often accurate estimation of GFR.

Results of our study bring us to conclusion that cystatin C serum concentration is a good marker of GFR. Besides, estimation of serum cystatin C is not technically difficult any more, but it is still more expensive than estimation of serum creatinine concentration. Correlation between CrEDTA clearance and serum cystatin C is better than correlation between CrEDTA clearance and serum creatinine. For more accurate role of cystatin C as new GFR serum marker further studies on some specific patient populations, also those with renal failure are needed (incipient renal failure, elderly etc.).

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