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Cystatin C as a marker of renal function in diabetic kidney disease

Abstract

Background. Serum cystatin C is a new promising marker of renal function. The aim of the study was to analyze serum cystatin C as a marker of renal function in diabetes patients.

Results. In 152 patients with type 1 and type 2 diabetes admitted to the department of internal medicine the serum cystatin C concentration was assessed. Glomerular filtration rate (GFR) was estimated based on the cystatin C concentration according to the Grubb formula and compared to GFR estimated based on serum creatinine concentration according to MDRD. They correlated strongly in patients with GFR lower than 60 mL/min/1.73 m² ($r = 0.62$, $P < 0.0001$).

In patients with GFR higher than 60 mL/min/1.73 m² the correlation was much weaker ($r = 0.24$, $P = 0.019$).

Conclusions. In patients with impaired renal function cystatin C seems not to have any advantage over serum creatinine in estimation of GFR. The advantage of cystatin C over serum creatinine may be found in early stages of diabetic kidney disease, when GFR is still normal or elevated. Cystatin C may be used for early prediction of renal function impairment in diabetic kidney disease.

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key words: diabetes, diabetic kidney disease, cystatin C, serum creatinine, glomerular filtration rate

Introduction

Diabetes is becoming the major single cause of end-stage renal disease in the world. Precise evaluation of renal function in early stages of diabetic kidney disease may indicate patients susceptible to progression to the end-stage renal disease. Intensification of the treatment in those patients might slow the progression of the disease. Implementation of behavior modification and pharmacological therapy targeted especially at hyperglycemia and hypertension declines urinary albumin excretion rate and decreases the progression to end-stage renal disease [1]. Intensive treatment is associated with increased life expectancy and is more cost-effective than conventional treatment in patients with diabetic kidney disease [2].

Progressive renal function decline in diabetes is an early event that occurs in a proportion of patients without increased albumin excretion rate [3]. The slope of

glomerular filtration rate changes over time, which suggests that it is a more proximal marker than microalbuminuria of a person's trajectory toward impaired renal function and ESRD [4]. Therefore, early renal function decline, rather than microalbuminuria, may be considered as an early marker of the committed process underlying progressive diabetic nephropathy [5].

Serum cystatin C might meet the need for detecting trends in renal function over time when GFR is normal or elevated [4]. Creatinine-based estimates of GFR seems to be good markers of renal function decline in advanced stages of diabetic renal disease when GFR drops below 60 mL/min/1.73 m².

The aim of the study was to analyze serum cystatin C concentration as a marker of impaired renal function in diabetes patients admitted to the department of internal medicine. Cystatin C-based estimates of GFR were compared to creatinine-based ones.

Material and methods

All diabetes patients hospitalized in the Department of Internal Medicine in the Teaching Hospital of the Medical University of Lodz were analyzed in 2007.

Serum cystatin C was determined using Cystatin C Immunoparticles kit (DakoCytomation, Denmark). The

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Table 1. Clinical characteristics of study population (N = 152)

Age (years)	59.6 ± 21.0
Gender (female/male)	62/90
Type 1/type 2 diabetes	34/118
Duration of diabetes after diagnosis (years)	11.4 ± 9.1
HbA _{1c} (%)	7.9 ± 1.8
Body mass index [kg/m ²]	27.7 ± 4.7
Hypertension (yes/no)	116/36
Coronary artery disease (yes/no)	80/72
Diabetic retinopathy (yes/no)	47/105
Diabetic neuropathy (yes/no)	29/123
C-reactive protein [mg/L]	9.0 ± 13.5
Diabetes treatment — only diet	18
Diabetes treatment — only oral agents	41
Diabetes treatment — oral agents plus insulin	12
Diabetes treatment — only insulin	81
Triglycerides [mmol/L]	1.8 ± 1.1
Total cholesterol [mmol/L]	5.0 ± 1.4
Smoking (yes/no)	63/89
ACE inhibitors or AT1 blockers (yes/no)	114/38

glomerular filtration rate (eGFR) was estimated based on serum cystatin C using the equation according to Grubb: $eGFR [mL/min/1.73 m^2] = 83.93 \times [cystatin C (mg/L)]^{-1.676}$ [6]. Serum creatinine was determined by Jaffe method and GFR was estimated using the Cockcroft-Gault equation [7] and the abbreviated MDRD (Modification of Diet in Renal Disease Study) equation: $eGFR [mL/min/1.73 m^2] = 186 \times [creatinine (mg/L)]^{-1.154} \times (age)^{-0.203} \times 0.742$ (for women) [8].

Exclusion criteria were renal replacement therapy or death during the hospitalization, hyperthyroidism, hypothyroidism, cancer, rheumatoid arthritis, newly diagnosed stroke, kidney tumor, polycystic kidney disease, > 10 leukocyte and erythrocytes per high power field in urine.

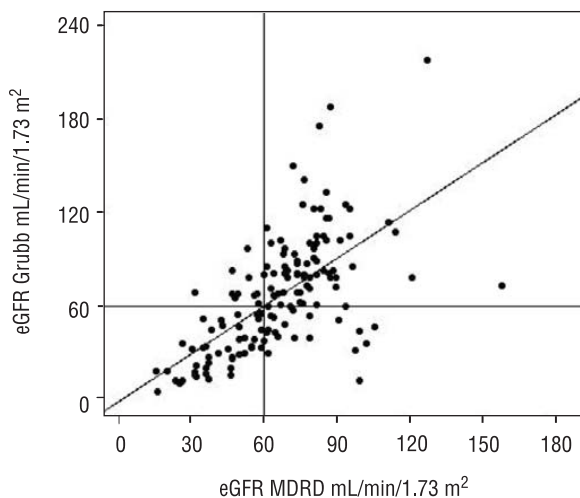
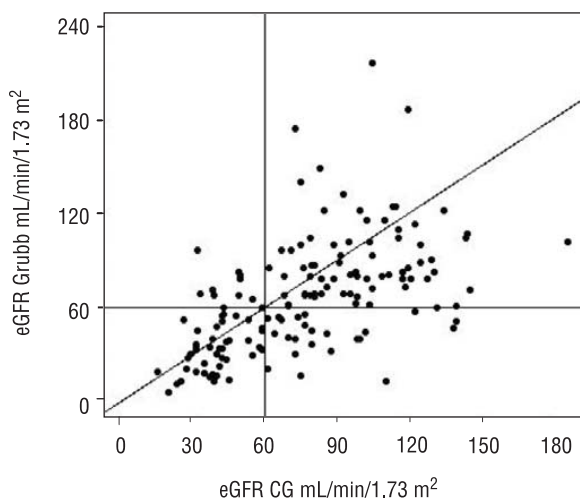
Statistical analysis was performed using software R version 2.7.0 from The R Foundation for Statistical Computing.

Results

Finally 152 patients, 34 with type 1 and 118 with type 2 diabetes, were analyzed. Clinical characteristics of study population is presented in Table 1.

Cystatin C based estimates of GFR according to Grubb correlated well with creatinine-based estimates of GFR. The correlation was stronger for MDRD equation (Fig. 1) than for Cockcroft-Gault one (Fig. 2).

We stratified the study population according to eGFR below and above 60 mL/min/1.73 m² based on the

**Figure 1.** Correlation between GFR estimated based on serum cystatin C according to Grubb and serum creatinine according to MDRD equation ($r = 0.62$, $P < 0.0001$)**Figure 2.** Correlation between GFR estimated based on serum cystatin C according to Grubb and serum creatinine according to Cockcroft-Gault equation ($r = 0.56$, $P < 0.0001$)

MDRD equation. A strong correlation was observed between eGFR based on Grubb and MDRD equation when eGFR was below 60 mL/min/1.73 m² ($n = 60$, $r = 0.62$, $P < 0.0001$). In subgroup with eGFR above 60 mL/min/1.73 m² much weaker correlation was observed ($n = 92$, $r = 0.24$, $P = 0.019$). The two correlation coefficients were significantly different ($P = 0.0046$). 22 patients had eGFR > 60 according to MDRD and < 60 according to Grubb (Table 2). 10 patients had eGFR < 60 according to MDRD and eGFR > 60 according to Grubb (Table 2).

Cystatin-C based estimated GFR correlated with the age of patients ($r = -0.51$, $P < 0.001$). With each year

Table 2. Comparison of the estimation of GFR based on serum cystatin C according to Grubb and serum creatinine according to MDRD

Creatinine-based eGFR	Cystatin C-based eGFR	
	> 60 mL/min/1.73 m ²	< 60 mL/min/1.73 m ²
> 60 mL/min/1.73 m ²	72	22
< 60 mL/min/1.73 m ²	10	48

eGFR dropped by 0.87 mL/min/1.73 m². The regression equation was: eGFR = 117.93 – 0.87 × age. No correlation with diabetes duration was observed. Positive correlation between cystatin C-based eGFR and HbA_{1c} was found in the whole study population ($r = 0.20$, $P = 0.012$). When patients were stratified according to the duration of diabetes, positive correlation between eGFR and HbA_{1c} was observed only when diabetes duration was 5 years or less ($r = 0.49$, $P < 0.001$). No correlation between eGFR and HbA_{1c} was observed in patients with diabetes duration longer than 5 years.

Discussion

Cystatin C has been introduced into clinical practice several years ago as a marker of renal function. Because serum creatinine concentration depends on other factors like muscle mass, estimation GFR based on serum creatinine may be biased. Using cystatin C should help to avoid this bias, however its advantages over serum creatinine are still discussed. Cystatin C measurement is more expensive than serum creatinine and therefore serum creatinine has not been widely replaced by cystatin C in clinical practice. Cystatin C might find its place in diabetic kidney disease, which is one of the most serious complications of diabetes. Only one third of diabetes patients are susceptible to diabetic kidney disease. The progression of the disease is slow and patients might be followed over many years before they develop end-stage renal disease or die. Mortality increases substantially with each stage of diabetic kidney disease. In type 2 diabetes patients with impaired renal function the chance to die is higher than to progress to the end-stage renal disease [9]. It has been proved that the progression of diabetic kidney disease might be slowed by improvement of glycemic control and by the treatment of hypertension. One of the major goals in diabetes care is to find patients at early stages of diabetic kidney disease and to intensify their treatment. We examined value of cystatin C in diabetic kidney disease, before introducing this test widely into clinical practice. We found that GFR estimated based on cystatin C correlated well with the GFR estimated based on serum creatinine in advanced stages of diabetic renal disease,

when GFR drops below 60 mL/min/1.73 m². GFR estimated based on serum creatinine using the MDRD equation was as good as GFR estimated based on cystatin C. However in patients with normal renal function there was a strong disproportion between GFR estimated based on cystatin C and serum creatinine. Cystatin C seems to be an accurate marker of GFR progression at stage 1 and 2 of chronic kidney disease and outperforms serum creatinine at GFR > 60 mL/min/1.73 m². Several previous studies suggested that serum cystatin C was advantageous compared with serum creatinine in the detection of mild diabetic kidney disease [10, 11].

When serum creatinine is used to estimate GFR National Kidney Disease Education Program (NKDEP) even recommends reporting values greater than or equal to 60 as “≥ 60”, rather than numeric values, because exact values above 60 are not reliable (<http://nkdep.nih.gov/>). From the practical point of view the exact estimation of renal function in the normal range seems to be less useful. But in diabetic kidney disease it might be very helpful in detecting trends of renal function impairment over time. In one study performed in type 1 diabetes patients serial measurements of cystatin C were more accurate than creatinine-based methods in detecting the decline of renal function [12]. A large prospective study is needed to definitively prove the advantages of cystatin C in detecting dynamics of renal function decrease in the normal range. A smaller study has already been performed [4].

National Kidney Foundation [13] and American Diabetes Association [14] recommend to examine serum creatinine once a year mainly to detect chronic kidney disease. Cystatin C might be better marker, not only in detecting of chronic kidney disease, but also in early prediction of diabetic kidney disease. Patients in whom fast progression of renal function decline is detected at early stages of diabetic kidney disease should be treated more intensively. There is no doubt that intensification of diabetes treatment decrease the risk of development and progression of microvascular complications [15, 16]. However, in some patients with long-standing diabetes complicated by cardiovascular diseases the risk of intensive diabetes treatment may overcome the advantages [17]. Therefore the goal of diabetes treatment should be set for each patient individually.

In the analyzed data positive correlation between cystatin C-based eGFR and HbA_{1c} was observed, but only in patients with diabetes duration 5 years or shorter. Observed positive correlation results rather from the correlation between glycemic control and hyperfiltration in the early stages after development of diabetes.

Increased HbA_{1c} is a proved risk factor of diabetic kidney disease, but we have not observed negative correlation between eGFR and HbA_{1c} in patients with diabetes duration longer than 5 years. It might result among others from cross-sectional study design.

Direct measurement of GFR is better than estimation of GFR. Inulin, iohexol, technetium-labelled diethylene triamine pentaacetic acid (99mTc-DTPA) and ethylene diamine tetraacetic acid (EDTA) offer better accuracy in measurement of GFR than estimation based on serum creatinine or cystatin C. However, all of the direct methods are expensive, time-consuming and require complex measurements. Therefore they are used mostly in the medical research and very rare in clinical practice.

Conclusions

There is no advantage of serum cystatin C over the creatinine-based GFR estimates in patients with advanced stages of diabetic kidney disease. Serum cystatin C seems to be a promising marker in estimation of renal function in early stages of diabetic kidney disease, when GFR is still normal or elevated.

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