Cistatin C – označevalec ledvičnega delovanja ter napovedovalec srčnožilnih bolezni in umrljivosti

Cystatin C – a marker of kidney function and predictor of cardiovascular disease and mortality

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Izvleček

Cistatin C v serumu je bil že pred desetletjem predlagan za označevalca ledvičnega delovanja. Trdni dokazi potrjujejo, da je ocena glomerulne filtracije s pomočjo cistatina C izboljšala prepoznavanje bolnikov s kronično ledvično boleznijo pri določenih populacijah. Enačbe za oceno ledvične funkcije, ki vključujejo standardizirano vrednost cistatina C v serumu so postale »state–of–the–art« določanja ledvične funkcije. Zadnje smernice za obravnavo bolnikov s kronično ledvično boleznijo tako vključujejo navodila in priporočila za uporabo cistatina C v klinični praksi. Rezultati raziskav kažejo, da je cistatin C več kot le označevalec ledvičnega delovanja, saj poda celostno informacijo o ogroženosti bolnikov, še posebej tistih z visoko stopnjo tveganja za razvoj srčnožilnih bolezni in dogodkov. Raziskave so pokazale tudi povezavo cistatina C z napredovanjem srčnožilnih bolezni.

Abstract

Over the past decade, serum cystatin C (SCC) has been often suggested as a marker of kidney function. Strong evidence has shown that SCC may improve classification of the glomerular filtration rate (GFR) to identify chronic kidney disease in certain clinical populations. SCC equations based on the SCC reference standard are considered state–of–the–art to estimate kidney function and the latest chronic kidney disease guidelines included several suggestions and recommendations that relate to SCC. The results of several previous studies have also suggested that SCC may be more useful than just a marker of GFR, as it may also be useful as a clinical marker to provide complementary information to established risk determinants, especially for high–risk populations. Additionally, other studies have reported that SCC may be a useful prognostic indicator of cardiovascular disease.

CYSTATIN C

Serum cystatin C (SCC) is a low molecular weight protease inhibitor that is produced by all nucleated cells at a constant rate and freely filtered across the glomerular membrane, reabsorbed, and then metabolized in the proximal tubule (1). The generation of SCC appears to exhibit a lower rate of interpersonal variability than that of serum creatinine and is not dependent on muscle mass (2). The relationship of SCC to direct measurement of glomerular filtration rate (GFR) appears to be influenced less by demographic characteristics and health status than serum creatinine levels. In certain clinical settings, SCC levels may be biased as a marker of kidney function, such as in patients with rapid cell turnover, uncontrolled thyroid disease, or a history of corticosteroid use (3,4). SCC concentration is a better indicator of GFR than serum creatinine concentration in patients with spinal injuries, liver cirrhosis, diabetes, mild to moderate impaired kidney function, and in elderly patients (5–7).

SCC AS A MARKER OF KIDNEY FUNCTION

Chronic kidney disease (CKD) is an important public health concern. In response to the rising prevalence of CKD, nephrologists and other physicians have focused on the prevention and early detection of renal failure. Estimation of GFR is essential for the evaluation of patients with CKD, which is defined as kidney damage or GFR < 60 mL/min/1.73 m^2 for ≥ 3 months, irrespective of cause, and classified into stages according to GFR. Therefore, GFR estimation allows the detection of early impairment of kidney function, the prevention further deterioration and complications, and correction of the dosage of drugs cleared by the kidney to avoid potential drug toxicity to facilitate management of CKD patients. The National Kidney Disease Education Program recommended reporting GFR values > 60 mL/min/1.73 m^2, not as an exact number, but simply as > 60 mL/min/1.73 m^2, and for values ≤ 60 mL/min/1.73 m^2, the exact numerical estimate should be reported (8).

Over the last few decades, several different markers for estimation of GFR have been proposed. The ideal marker of GFR should be an endogenous molecule that is produced at a constant rate and cleared solely by the kidneys via free glomerular filtration, without being either secreted by tubular cells or reabsorbed into the peritubular circulation. The "gold standard" for estimation of GFR is clearance of exogenous substances, such as inulin, iohexol, chromium–51 ethylene diamine tetra-acetic acid, technetium–99m diethylene triamine penta–acetic acid, and iodine–125 iothalamate. However, these techniques are time–consuming, labor–intensive, expensive, and require administration of substances that make them incompatible with routine monitoring. In clinical practice, as in most studies, serum creatinine has become the most commonly used marker to estimate GFR, despite several known disadvantages (9). The current Kidney Disease Outcomes Quality Initiative guidelines emphasize the need to assess kidney function using predictive equations, such as the Chronic Kidney Disease Epidemiology Collaboration equation (CKD–EPI formula) and propose SCC as marker of GFR to improve CKD classification based on the estimated GFR (10,11).

Over the last few years, many other SCC–based equations (cystatin C formulas) have been developed to estimate the GFR from SCC concentrations and compared to serum creatinine–based formulas (12–18). The results of several published studies suggest that the SCC–based prediction equations, which require just one variable (SCC concentration), achieved a diagnostic performance that was at least as good as the serum creatinine formulas, which included a very sophisticated serum creatinine–based equation that uses both serum creatinine and SCC (CKD–EPI creatinine and cystatin formula) (13,14,19–21). The simple cystatin C formula overrides the well–known tendency of serum creatinine–based formulas or combined formula to underestimate the GFR and can lead to unnecessary diagnostic and therapeutic strategies regarding the stage of CKD. The most recent and sophisticated CKD–EPI formulas require additional equipment, which is unnecessary when using the simple cystatin C formula (21–23). The studies have demonstrated that the simple cystatin C formula may

be useful to evaluate renal function in overweight patients with type 2 diabetes mellitus and impaired kidney function, as well as for elderly patients with CKD in daily clinical practice in hospital and, especially, outpatient settings (21–23). Despite the advantages of the simple cystatin C formula, SCC–based equations cannot completely replace the "gold standard" for estimation of the GFR in populations with CKD, but may contribute to more accurate selection of patients requiring such invasive and costly procedures.

Recently, Shlipak et al. (4) stressed three potential strategies for SCC screening. In persons with borderline estimated GFR with serum creatinine, persons at high risk of CKD, and those with conditions known to render serum creatinine levels insensitive for detecting CKD (hospitalized patients with malnutrition, malignancy, and elderly) estimation with SCC should be helpful. The requirement for procedures, such as chemotherapy, surgery, or angiography is a situation in which determining kidney function with SCC may be important to ameliorate the risk of complications. SCC should be monitored in patients with chronic conditions associated with a high prevalence of CKD, including those with cardiovascular disease (CVD), heart failure, diabetes, and hypertension, as well as kidney transplant recipients (4).

CYSTATIN C AS A PREDICTOR OF CARDIOVASCULAR DISEASE AND MORTALITY

Coronary heart disease and stroke are the main forms of CVD and are leading causes of death worldwide (24,25). Renal dysfunction carries a substantial risk for cardiovascular morbidity and mortality, which was first demonstrated in patients with end–stage renal disease. Reportedly, CVD begins during the earlier stages of CKD and the risk for CVD increases with decreased kidney function (26–29). An independent, graded association was observed between renal dysfunction estimated by GFR and the risk of death, cardiovascular events, and hospitalization in a large, community–based population (29). Furthermore, previous studies have shown that renal impairment is an independent risk factor for CVD and total mortality (30,31). Moreover, decreased GFR has been found to be an independent risk factor in patients with diabetes and congestive heart failure for future CVD events and total mortality (32,33). In addition, percutaneous coronary interventions also have a less favorable outcome for patients with CKD (34). In patients with acute coronary syndrome after percutaneous coronary intervention, a higher stage of renal dysfunction was directly associated with higher mortality (35). In a meta–analysis by Lee et al. (36), renal dysfunction was defined as estimated GFR < 60 mL/min/1.73 m^2 and independently associated with the incidence of ischemic and hemorrhagic stroke. In a prospective study of 390 Caucasian adult patients (35–96 years of age) after ischemic stroke, the authors demonstrated that those with renal dysfunction were at a higher risk for long–term cardiovascular events and total mortality. Furthermore, patients with ischemic stroke and renal dysfunction are also at higher risk for future cardiovascular morbidity (37).

Among the known markers to estimate kidney function, SCC may have prognostic importance as a predictor of adverse outcomes independent of renal function. Previous studies have reported that compared to estimated GFR by serum creatinine concentrations, estimated GFR with SCC demonstrated a stronger and more linear association with hard outcomes, such as all–cause mortality, cardiovascular mortality, and cardiovascular events (38,39). Koenig et al. (40) evaluated the impact of SCC and other markers of renal impairment on prognosis in a large cohort of 1033 patients (30–70 years of age) with coronary heart disease. The cohort was followed for nearly 3 years and the primary outcome was a combined endpoint of fatal and nonfatal cardiovascular events (myocardial infarction, cerebrovascular accidents, transient ischemic attacks, or death attributable to CVD). During the follow–up period, 7% of the study participants experienced a cardiovascular event; however, there was no significant association with serum creatinine levels. In contrast to serum creatinine, greater SCC levels were associated with an increased risk of cardiovascular events, even after adjusting for well–known risk factors, including body mass index, smoking history, high density lipoproteins–cholesterol, diabetes, education level, family

status, history of myocardial infarct, and number of affected vessels at baseline, as well as the inflammatory marker C–reactive protein (40). Compared with individuals in the lowest quintile of SCC, those in the highest quintile had more than a two–fold increase in risk of cardiovascular events, even after adjusting for estimated serum creatinine clearance (41). Also, a study from the PREVEND investigators suggested that higher SCC concentrations increased the overall risk of death (42). Higher SCC levels were also associated with higher mortality in patients with acute coronary syndromes, new onset of congestive heart failure, and the elderly (43–45). A report by Jarnberg et al. (43) first demonstrated that monitoring SCC levels substantially improved the early risk stratification of a large population of patients with suspected or confirmed non–ST–elevation acute coronary syndrome. When 726 patients were divided according to final diagnosis into three groups (those with non–ST–elevation acute coronary syndrome, other cardiac risk factors, and those with other noncardiac or unknown causes), the prognostic value of SCC was evident in all groups. When adjusted for other well–known predictors of outcome (age, diabetes, troponin T, N–terminal pro–brain natriuretic peptide, and C–reactive protein), the SCC level remained an independent predictor of mortality. In a comparative study of markers of renal function (serum creatinine and serum creatinine clearance calculated from the Cockcroft–Gault equation) by receiver–operating curve analyses, SCC had the best ability to discriminate between survival and death. When patients were categorized into quartiles for each marker, the fourth quartile of SCC was associated with a 12–fold increase in mortality compared with the first quartile. For serum creatinine clearance and serum creatinine, the highest quartiles demonstrated a six– and three–fold increase in mortality, respectively, compared with the lowest quartiles (43). In recent studies, where new and more precise equations based on serum creatinine and SCC or both were used, some differences between markers of GFR estimation in prediction of mortality in different patient populations were observed (46,47). Estimated GFR based on serum creatinine appeared to have J–shaped association with the risk of death. On the contrary, estimated GFR based on SCC showed a linear association with mortality. GFR estimated from both serum creatinine and SCC was significantly more predictive of outcomes than estimated GFR by serum creatinine, but significantly less predictive of outcomes than estimated GFR by SCC alone (46,47). The reason for these differences was not completely clear, but can be partly explained by the non–GFR determinants of SCC (48).

A strong association was reported between renal function and mortality that could be explained by the atherosclerotic process in arteries (49). However, SCC levels were also independently associated with mortality in patients without cardiovascular–related causes of their symptoms, thereby indicating that the association between renal function and atherosclerotic processes is not solely responsible for the increased mortality observed at higher SCC levels (43). Since the mechanisms behind these suspected associations remain unclear, further attention is warranted.

CONCLUSIONS

The present review highlighted the role of SCC for early identification of patients with renal impairment and prediction of cardiovascular events. Based on the evidence, the authors encourage clinicians to incorporate SCC into daily practice as renoprotective measures and defence against cardiovascular events.

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