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REVIEW ARTICLE

Identification of cystatin C as a new marker of glomerular filtration rate, and of shrunken pore syndrome – a new kidney disorder defining selective glomerular hypofiltration syndromes – calls for expansion of the international KDIGO guidelines

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ABSTRACT

Cystatin C was identified as a marker of glomerular filtration rate (GFR) in 1979, and the parallel analysis of cystatin C and creatinine led to the identification of shrunken pore syndrome (SPS) – a new kidney disorder – in 2015. Since then, it has been shown that cystatin C in many aspects is superior to creatinine as a marker of GFR and cardiovascular risk. SPS, an entity within the selective glomerular hypofiltration syndromes (SGHS), has been demonstrated to be associated with a strong increase in morbidity and mortality in several populations. Despite the seriousness of SPS and SGHS, and the availability of potential treatments, many patients with these conditions remain undiagnosed, due to the limitations of the international Kidney Disease Improving Global Outcomes Organization (KDIGO) guidelines. Given the significant clinical advantages of cystatin C in diagnosing and treating kidney disorders, there is a need to expand the KDIGO guidelines to include cystatin C measurements alongside creatinine at least in the initial patient evaluation but also in follow-up evaluations. This would improve the early detection and management of patients with kidney diseases, ultimately enhancing patient outcomes. The present discourse summarizes the development of this understanding from the original observations in 1979 and 2015 to the latest findings.

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cystatin C; kidney; glomerular; morbidity; mortality; renal; KDIGO

Introduction

To recognise the rationale for expanding the KDIGO diagnostic guidelines by adding cystatin C- to creatinine-analysis in at least the initial diagnostic process, we describe the history of scientific evolution of concepts based upon the use of cystatin C measurements. We consider the decisive argument for expanding the KDIGO guidelines is that without such an update, a significant proportion of all patients with kidney disorders, namely those suffering from selective glomerular hypofiltration syndromes without increased creatinine levels, will be undiagnosed and miss benefits from available treatments.

Cystatin C as a marker of GFR

Cystatin C, a small 13.3 kDa protein, was initially identified as a marker of glomerular filtration rate (GFR) in 1979 [1] and validated by three subsequent follow-up studies conducted by the same research group in 1985 [2–4]. One of these studies [2] indicated that other proteins, in addition to cystatin C, namely complement factor D, 23.7 kDa, and β_2-microglobulin, 11.7 kDa, could be used as GFR-markers, but that cystatin C was the superior marker. The study also found that muscle mass does not significantly influence the cystatin C level as the correlation between cystatin C and GFR did not differ between men and women [2]. The low influence of muscle mass on cystatin C levels suggested that reliable cystatin C-based GFR-estimation equations could be constructed, without the use of controversial muscle-related parameters such as race and sex. Such equations have also been constructed and are frequently used [5–8]. The minimal impact of muscle mass, as initially shown in 1998 [9], implies that the cystatin C reference values for children and adults are comparable in contrast to creatinine reference values.

Reliable international use of a marker for GFR requires the availability of an international reference material 'calibrator' and such a material for cystatin C, ERM-DA471/IFCC, was developed 2008–2010 [10–13] and is available from international calibration centres, e.g. the European Commission's Joint Research Centre.

Several early comparisons between cystatin C and creatinine as markers of GFR indicated that cystatin C outperformed creatinine in several populations [14–18], especially those with sarcopenia [19], whereas it was less accurate in patients treated with moderate to high doses of glucocorticoids [20].

Cystatin C- and creatinine-based GFR estimating equations. Optimal combination. Lund model

In clinical practice, it is more useful to work with the estimated GFR derived from cystatin C or creatinine levels, rather than the actual substance levels themselves. Creatinine- and cystatin C-based GFR estimating equations, e.g. [21–25], have therefore been used for several decades. Equations combining creatinine and cystatin C were introduced in 2006 and are frequently used, as they display a better accuracy expressed as P_{30}-values, than equations using only one of the parameters [26–32]. However, equations combining creatinine and cystatin C are not optimal for clinical use as their accuracy will be disturbed by non-renal factors influencing either one or both of creatinine and cystatin C. In clinical practice, it is therefore more useful to separately run both a cystatin C and a creatinine-based estimating equation and compare the two estimates, $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$ [33]. If they agree within a specified limit, the arithmetic mean, ($eGFR_{cystatin\ C}$ +

$eGFR_{creatinine}$)/2, of the two estimates is used and has been shown to display at least the same accuracy as the estimates of more complex equations containing both parameters [33,34]. The model, with separate estimations for the two GFR-markers, has then been refined and used for new diagnostic purposes [35,36]. The specified limit for the agreement influences the accuracy and reliability of the mean and can be adjusted for the specific patient concerned. For example, when using estimated GFR for adjusting medication dosage, particularly of medications with potential adverse side effects, a higher degree of agreement between $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$ is required [33,34]. If non-renal factors influencing one of the two parameters are present, the GFR-estimating equation based upon the other parameter is used [33]. This model for estimation of GFR, called the Lund model, has been used in Sweden since 2009 [33,34]. In those few instances when $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$ have agreed, but disagreed with a simultaneous invasive determination of GFR, the discrepancy has always been due to an error in the invasive determination, rather than in the estimation model, when the cause for the disagreement could be determined [33]. The average of $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$, when in agreement, can therefore be considered at least as reliable as an invasive determination of GFR and, hence, a useful tool to reduce the number of required such invasive examinations [33,34].

Cystatin C and $eGFR_{cystatin\ C}$ are superior to creatinine and $eGFR_{creatinine}$ as indicators of mortality and morbidity

Two pioneering studies, published in 2004 and 2005, that included older patients with suspected acute coronary syndrome or other types of cardiovascular disorders, found that cystatin C was superior to creatinine in predicting cardiovascular events (CVE) and mortality [37,38]. Since then, numerous investigations concerning virtually all types of populations have demonstrated that cystatin C or $eGFR_{cystatin\ C}$ is superior to creatinine and $eGFR_{creatinine}$ in predicting CVE and mortality [39–42].

Initially it was assumed that the superiority of cystatin C and $eGFR_{cystatin\ C}$ in predicting mortality and morbidity was because they in most populations are superior to creatinine and $eGFR_{creatinine}$ in estimating GFR [38]. However, additional studies, in which GFR was carefully measured, demonstrated that measured GFR was not superior to cystatin C in predicting mortality [43]. Thus, other reasons had to be found for the superiority of cystatin C in predicting mortality and morbidity. A statistical correlation between cystatin C and C-reactive protein (CRP) in a large population was suggested to prove that inflammatory processes cause an increase in cystatin C [44], unrelated to a decrease in GFR. The ability of cystatin C to identify both inflammatory disease and kidney disease would thus make it superior to creatinine in predicting morbidity and mortality [44]. But studies in elective surgery patients and in critically ill patients clearly demonstrated that inflammation per se does not cause an increase in cystatin C [45–47]. The correlation observed between CRP and cystatin C is therefore probably driven by the ascertained link between CRP and development of atherosclerosis [48] and the associated decrease in GFR. Given the limitations of previous explanations, a new hypothesis seemed to be required to elucidate the underlying pathophysiological background to the superiority of cystatin C and $eGFR_{cystatin\ C}$ to creatinine and $eGFR_{creatinine}$ in predicting morbidity and mortality.

Discovery of shrunken pore syndrome (SPS) and selective glomerular hypofiltration syndromes (SGHS)

After the Lund model for estimation of GFR (based upon simultaneous use of $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$) was introduced in clinical practice in 2009 [33,34], a study in 2015 discovered that significant differences between $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$ were common even in the absence of known non-renal factors influencing creatinine or cystatin C levels [49]. The dominating difference was a lower $eGFR_{cystatin\ C}$ than $eGFR_{creatinine}$, and thus an $eGFR_{cystatin\ C}$/$eGFR_{creatinine}$-ratio below 1.0 [49]. A selective decrease in the filtration of cystatin C (13.3 kDa) compared to that of creatinine (0.11 kDa) had previously been revealed in pregnancy [50–54] and since a shrinking of the pores in the pore model for glomerular filtration would explain such a phenomenon, the condition in males and non-pregnant females was given the name 'shrunken pore syndrome' (SPS) [49]. The studies of glomerular filtration in 2015 [49] demonstrated that the filtration of 10–30 kDa molecules, such as cystatin C, β_2-microglobulin, beta-trace protein, and retinol binding protein could be concomitantly and selectively reduced in the presence of normal filtration of molecules < 1 kDa, such as creatinine and water. It had also been observed that the selective decrease in filtration of 10–30 kDa molecules in pregnancy was more pronounced in the pathological condition pre-eclampsia [53,54].

Shortly after the discovery of SPS, multiple studies published in 2016 found that SPS was associated with a significant increase in mortality and/or morbidity [55–59]. Since then, numerous articles, concerning the association between a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio and mortality and morbidity, have continuously been published [60–71]. An important observation is that a decreasing $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio is associated with increasing mortality and morbidity without threshold levels [62,70,71].

About five years after SPS was first described in 2015 and characterized by a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio [49] the same type of syndrome was identified using a negative difference between $eGFR_{cystatin\ C}$ and $eGFR_{creatinine}$ [72]. This way of identifying SPS has since then often been used [73–76], but it has no advantages in predicting mortality over the original way to identify the syndrome by a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio [77].

Investigations in 2021 of the glomerular basement membrane thickness in diabetic kidney disease identified that membrane thickening, accompanied by elongation of the pores, also lead to a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio, indicating that not only shrinking, but also elongation, of the pores in the membrane causes a selective decrease in filtration of 10-30 kDa compared to smaller molecules (< 1 kDa), such as creatinine and water [78]. It was therefore obvious that both SPS and elongated pore syndromes should be considered as special cases of a more comprehensive group of kidney disorders tentatively called 'selective glomerular hypofiltration syndromes' (SGHS) [78–82].

Limitations of the current KDIGO guidelines in diagnosing selective glomerular hypofiltration syndromes have been identified, resulting in missed opportunities for treatment

Many patients with selective glomerular hypofiltration syndromes will not be diagnosed using the present KDIGO guidelines, which thus also will fail to identify a significant portion of all kidney disorders, including some with high risk for mortality that could benefit from treatment. According to the international KDIGO guidelines diagnosing chronic kidney disease requires a decrease in measured or estimated GFR and/or the presence of albuminuria [83]. However, a careful and detailed study from 2020 of 2,781 individuals with measured GFR, known diagnoses, known causes of death during a median of 5.6 years, strongly indicated that the KDIGO guidelines are insufficient in identifying all kidney disorders [70]. The study used an $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio <0.70 to identify individuals with SGHS [70]. As expected, the SGHS subpopulation of 645 individuals displayed a significant increase in mortality with a hazard ratio (HR) of 3.0 compared to individuals with a ratio ≥ 1.00 [70]. Among the subcohort of 1300 individuals with normal measured GFR, 17% (221 individuals) had an $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio <0.70 and a HR of 4.1 compared to individuals with a ratio ≥ 1.00 [70]. Thus, applying the KDIGO guidelines, these 221 individuals with normal GFR are undiagnosed with SGHS. The number of patients with SGHS not identifiable by the KDIGO criteria was not only the 221 among the 1300 with normal GFR, but the KDIGO criteria also leaves 424 among the 1481 with reduced measured GFR, corresponding to about 29%, undiagnosed.

A conspicuous and surprising observation was that among the 567 individuals with no signs of disease and with normal GFR ('healthy' individuals), 11.5% (65 individuals) displayed SGHS with a HR for mortality of 7.3 compared to individuals with a ratio ≥ 1.00 [70]. These 65 individuals represent 65/2781, or 2.34%, of the totally investigated population and suffer thus from SGHS undiagnosed by the present KDIGO guidelines. If the population of 2781 is approximately representative for the total Swedish population of about 10 500 000, about 246 000 individuals of this population suffer from SGHS undiagnosed by the present KDIGO guidelines. This is, in addition, an underestimation of the number, since a significant part of the studied population, although unhealthy, also suffers from SGHS undiagnosed by the present KDIGO guidelines as shown above.

SGHS is a kidney disorder *inter alia* as it concerns an abnormally low glomerular filtration of a significant part of the human proteome [49,59,60,70,77–80] and is associated with severe clinical consequences [53–80]. The study by Åkesson et al. [70] therefore demonstrates that the present KDIGO guidelines are insufficient for diagnosing a significant part of all kidney disorders and not optimal for calculation of HR. It is noteworthy that several studies of SGHS indicate that the diagnosis is valid for individuals who are considered healthy and/or do not meet the KDIGO guidelines for kidney disease [56,57,70,71,77,80].

The pathophysiology of SGHS and possible treatment strategies

When SPS initially was described in 2015, it was shown that the filtration of 10-30 kDa molecules, such as cystatin C, β_2-microglobulin, and beta-trace

protein, was selectively reduced compared to a normal filtration of molecules < 1 kDa [49]. Subsequently, it was demonstrated that the general accumulation of proteins < 30-40 kDa in the proteome of individuals with SPS also meant an accumulation of atherosclerosis-promoting proteins in plasma [60,84]. It is known that glomerular filtration strongly influences the human proteome [85] and in particular proteins < 30-40 kDa, which represent about 40% of the human proteome [79]. Not only shrinking of glomerular pores [49], but also elongation of them, e.g. in glomerular basement membrane thickening in diabetes [78], will cause a selectively reduced filtration of 10-30 kDa molecules compared to moleules < 1 kDa according to the pore model for glomerular filtration [79,80]. It is therefore apparent that not only SPS but also elongated pore syndrome is part of a more extensive group of kidney disorders tentatively called selective glomerular hypofiltration syndromes (SGHS) [77–82]. Earlier studies had shown that a similar type of selective glomerular hypofiltration develops during normal pregnancy [50–52] and more extensively in preeclampsia [53,54]. It should also be noted that direct measurement of renal extraction of 0.06 – 150 kDa substances supports selective glomerular hypofiltration as a pathophysiological mechanism [86,87]. The observation that the reduced elimination of 5–30 kDa proteins in preeclampsia and normal pregnancy returns to normal about 2 months after delivery, indicates that the pathophysiological process of SGHS might be reversible [88].

Although the causes of SGHS are unknown, the hypothesis that accumulation of atherosclerosis-promoting proteins might play a role in the pathophysiology [60,84] and the fact that the process is reversible in pregnancy [50–54,88] suggest possible ways of treatment. Since accumulation of 5-30 kDa proteins promoting development of atherosclerosis and with other possible harmful effects seems to be a pivotal process in SGHS, several treatment modalities are conceivable. When further studies will identify the most pertinent of the accumulated harmful proteins, the levels of these proteins could be reduced by use of monoclonal antibodies or their effects inhibited by use of receptor antagonists.

Kidney transplantation might impact the distortion of the proteome in SGHS in a positive way. It is, in connection with this treatment suggestion, of some urgency to investigate if kidneys from patients with normal $eGFR_{creatinine}$ and/or normal measured GFR and reduced $eGFR_{cystatin\ C}$, thus suffering from SGHS, will work as fine for donation as kidneys from healthy individuals without SGHS.

Interestingly, a recent study reports that diet seems to influence the mortality or morbidity of SGHS [89]. Dietary interventions might therefore be a possible way of reducing the clinical effects of SGHS.

Future studies will have to evaluate the effect in SGHS of kidney sparing treatments like ACE-inhibitors, angiotension-II-receptor-blockers, SGLT2-inhibitors, non-steroidal mineralocorticoid receptor antagonists, endothelin receptor antagonists etc.

Although no treatment is established for SGHS, the syndromes represent risk factors for unfavourable consequences of kidney disorders. This knowledge is useful in the optimal selection of treatments required by the specific pattern of risk factors in an individual.

Recommendation to expand the KDIGO guidelines to allow diagnosing selective glomerular hypofiltration syndromes (SGHS), including shrunken pore syndrome (SPS), and improved estimation of GFR and prediction of mortality

A dramatic increase in patients with need for dialysis has been noticed for several decades. The Kidney Disease: Improving Global Outcomes organization was established in 2002-2003 with the mission to improve the care and outcomes of people living with kidney disease worldwide [83,90–92]. An important part of this endeavour has been to establish efficient uniform criteria for diagnosing kidney disease [83,90–92]. Although this effort has been largely successful, it has been slow in adopting the demonstrated clinical advantages of cystatin C as a diagnostic tool. In the original KDIGO guidelines of 2002 cystatin C is mentioned 6 times, and the recommendation is 'conflicting results make the available data inadequate for recommending cystatin C measurement for widespread clinical application' [90]. In the KDIGO guidelines on glomerular diseases of 2021 cystatin C is mentioned 7 times and the recommendation is 'Serum cystatin C, as an alternative to Serum creatinine, has not been well validated in subjects with GN' [91]. These recommendations were surprising as in 2021 about 5400 articles on cystatin C and kidney disorders had been published, among them articles showing the superiority of cystatin C over creatinine in estimating GFR [14–19], and in predicting the mortality of kidney disorders [37–41,43] and its use in diagnosing SPS with its high mortality [49,55–62]. International reference material for cystatin C has been available since 2010 [10–13].

However, in the KDIGO recommendations on management of chronic kidney disease from 2013,

cystatin C is mentioned 159 times, and the general suggestion is' We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate' [92]. In the KDIGO guidelines on management of chronic kidney disease from 2024 [83] cystatin C is mentioned 214 times, and the general recommendation is' If cystatin C is available, the GFR category should be estimated from the combination of creatinine and cystatin C (creatinine and cystatin C–based estimated glomerular filtration rate [eGFRcr-cys]) [83]. Furthermore, the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease recommended in 2021 national efforts to facilitate increased, routine and timely use of cystatin C [93].

So, although the latest KDIGO guidelines concerning use of cystatin C are less restrictive, they still fall short of optimal. Specifically, they do not highlight the general superiority of cystatin C, or cystatin C based GFR estimating equations, over creatinine, or creatinine based GFR estimating equations in estimating GFR and in predicting mortality in many populations. The current guidelines also have a more serious consequence: they will miss diagnosing SGHS, for example SPS, in many patients with normal $eGFR_{creatinine}$, thereby failing to identify their kidney disorder and its high mortality, which might be reduced by available treatments. We therefore strongly advocate for updated KDIGO guidelines incorporating simultaneous analysis of both cystatin C and creatinine at least at the primary patient consultation to ensure optimal diagnosis and treatment of kidney disease (Figure 1).

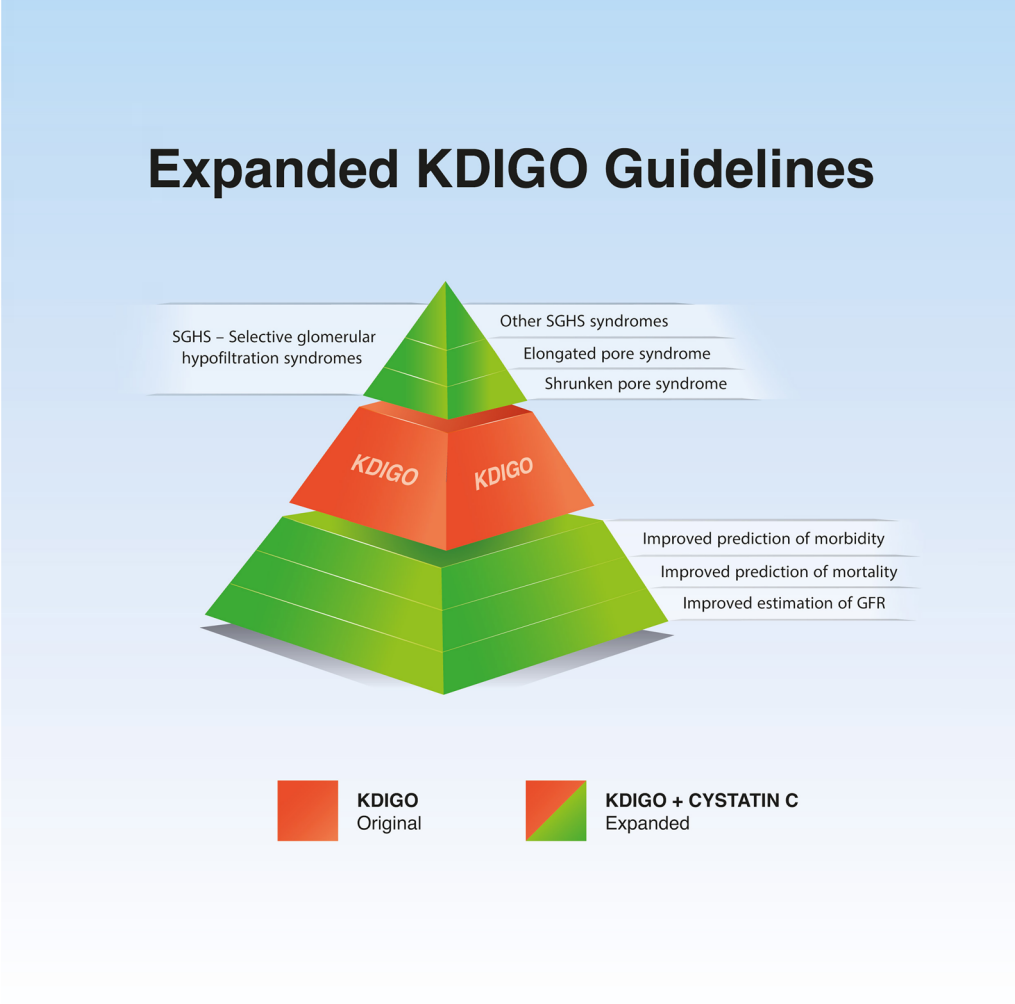

Figure 1. If cystatin C is added to the original KDIGO guidelines, the diagnostic capabilities will be expanded by allowing detection of Selective Glomerular Hypofiltration Syndromes (SGHS), including Shrunken Pore Syndrome (SPS) and elongated pore syndrome. Estimation of GFR will also be improved and reach the reliability of invasive determination of GFR. In addition, the prediction of morbidity and mortality will be significantly enhanced. *Medical artist: Lotta Heinegård*

Cost arguments against use of cystatin C are invalid

Several reviews of GFR estimation have argued that cystatin C cannot be generally used as the cost of the analysis is too high [94–96]. However, the initial high prices for cystatin C do not correspond to the simple reagents required for the test, which are like the reagents used for analysis of other frequently used tests for plasma or serum levels of e.g. CRP, antitrypsin, apolipoprotein B, haptoglobin, IgG, insulin, and thyrotropin. The price for cystatin C has therefore generally become lower and can be expected to be stabilised at the same level as these other commonly used and affordable tests.

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Disclosure statement

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