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Review Article

The role of cystatin C in the risk of hip fractures in the elderly

Konstantina Papakonstantinopoulou[1], Ioannis Sofianos[2]

[1]Department of Nephrology, Korgialeneio- Benakeio Hospital, Athens, Greece; [2]Department of Rheumatology, Asklipieio Voulas General Hospital, Athens, Greece

Abstract

World's population is aging. The elderly are at high risk for both chronic kidney disease (CKD) and hip fractures. Severe chronic kidney disease is a well-known risk factor for fractures and death especially in the elderly. Mild and moderate stages of kidney disease are often undiagnosed and/or untreated, thus their effect on fracture risk is not well established. Many ways of estimating glomerular filtration rate (GFR) have been developed but there are very few studies recommending the best and most valuable method for estimated GFR (eGFR) calculation that could correlate with fracture risk. In this mini- review we searched the literature concerning the use of cystatin C in the estimation of GFR related to the risk of hip fractures in the elderly. Our goal was to review the most important recent evidence on whether cystatin C could become a useful biomarker for the prediction of fracture risk. We concluded that there is evidence to support the use of cystatin C in hip fracture risk prediction in elder patients with chronic kidney disease.

Keywords: Cystatin C, Creatinine, Hip fractures, Chronic kidney disease (CKD), Glomerular filtration rate (GFR)

Introduction

The world's population is aging. It is estimated that in a period of time between 1990 and 2050 the number of people over 65 years will have increased substantially[1]. Osteoporosis[2] and Chronic Kidney Disease have increased prevalence in the elderly (almost a quarter of people of more than 70 years old have moderate kidney disease)[3] leading to decreased bone strength and consequently to more fractures[4]. This high incidence of fractures in the elderly increases mortality as well as disability and represents an economic burden for the health system of every society worldwide[5]. Severe chronic kidney disease is a well-known risk factor for hip fractures, not only osteoporotic (related to age, menopause, falls, history of fractures etc.) but also due to renal osteodystrophy, a condition nowadays known as Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)[4]. Dual- energy X-ray absorptiometry (DXA) is not reliable for predicting fracture risk in this special patient category. In fact it may be low, normal or high in each of the major types of CKD- MBD -namely hyperparathyroidism, adynamic bone disease, and osteomalacia-, without being an adequate assessment tool for estimating fracture risk[4]. The importance of the effect of mild to moderate kidney disease on fracture risk is not well studied because earlier stages of kidney disease are unrecognized[6]. Consequently, research has concentrated on finding a biomarker that predicts with accuracy the risk of hip fractures in CKD patients. There is an ongoing debate over which bio- molecule is optimal for the calculation of glomerular filtration rate (GFR) and, therefore, the chronic kidney disease staging. This may be important at the time to estimate fracture risk. Creatinine is typically used in the majority of eGFR calculation equations, but there is also a high interest on behalf of the investigators on whether the use of cystatin C in the field of fracture risk estimation is preferable.

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Corresponding author:
Konstantina Papakonstantinopoulou, Korgialeneio-Benakeio Hospital, Athanasaki 2, 11526, Athens, Greece

E-mail: *konstantina.smad@gmail.com*

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Cystatin C

Cystatin C is a 13-kDa protein of 122 amino acids, member of the cysteine proteinase inhibitor family[7], found in almost all nucleated human cells[6,8,9], and its gene is of the housekeeping type which is compatible with a stable production rate by most cells[6,8-10]. There has not been found any correlation of cystatin C to any pathological state other than GFR[10]. The plasma levels of cystatin C reflect the sum of diet and cell production minus kidney, gut and liver elimination[10]. It is a useful tool used for the estimation of GFR because it is freely filtered by the glomerulus and is independent of sex, race and muscle mass making it perfect for use in the elder population (where due to reduced muscle mass the use of creatinine overestimates GFR)[10] and in recognizing better than serum creatinine moderate stages of chronic kidney disease[11]. It is measured with using automated latex particle-enhanced turbidimetry assays, or through a latex particle-enhanced nephelometric immunoassay (PENIA)[10], its cost is US $3.00 versus the US $0.25 cost of creatinine[10] and has a serum reference range of 0.51- 0.98 mg/L[12].

Chronic kidney disease and the risk of fractures

Advanced age can cause renal function decline[13]. Chronic Kidney Disease is a risk factor for hip fractures, the latter considered having a heavy impact on any health system[6,13-15] especially when it comes to patients with End Stage Renal Disease (ESRD)[16]. Moreover, CKD patients have greater incidence of frailty and falls, leading to fractures as well[17]. Apart from the incidence of osteoporosis, CKD patients also suffer from other metabolic bone diseases, known under the before-mentioned "umbrella" term of CKD- MBD (termed until recently as Renal Osteodystrophy)[4] that includes osteitis fibrosa, osteomalacia, adynamic bone disease and a mixed variant[18]. The manifestations of CKD-MBD can be the result of any combination of: a) parathyroid hormone (PTH), calcium, phosphorus and vitamin D balance abnormalities, b) pathologic turnover, mineralization and bone volume and c) vascular calcification[4]. Key role in the risk of fractures in this population except from age, female gender and low body mass index (BMI) are secondary hyperparathyroidism, metabolic acidosis and low levels of vitamin D (both 25- OH and 1,25-OH Vitamin D3)[16,19]. Although there is a positive correlation between fractures and severe CKD, as well as End Stage Renal Disease, the relation with mild and moderate forms of kidney disease in the elderly is not well established[7] probably because less severe CKD frequently remains undiagnosed[3]. The most widely accepted classification categories of CKD as for today is Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD based on GFR which is shown in Table 1[20].

G1	Normal or high	≥90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	<15

Table 1. GFR categories (ml/min/1.73m^2), Retrieved from KDIGO 2012[14].

Glomerular filtration rate

Glomerular filtration rate (GFR) is the rate at which a substance is filtered from the glomeruli (ml/min). GFR can be estimated via equations (estimated GFR, eGFR) or by measuring the clearance of a serum molecule that is filtered freely from the glomeruli while neither secreted nor reabsorbed by the renal tubules. Such molecules can be exogenous (e.g. inulin) or endogenous (e.g. creatinine, cystatin C)[19]. Equations for eGFR are the Cockcroft- Gault equation (overestimating GFR in patients with obesity or edema), the Modification Diet in Renal Disease Study (MDRD) equations (more accurate for lower values of GFR) and the Chronic Kidney Disease[21] Epidemiology Collaboration (CKD-EPI) equations (precise even in higher values of GFR)[19]. Creatinine is mostly used in every day's clinical practice, however its production depends on muscle turnover, protein consumption and physical activity[8] factors that make it rather inappropriate for accurate measurement of GFR in several patient categories, like the elderly. Cystatin C measurement is superior to that of creatinine for GFR estimation, because cystatin C is independent of muscle mass and protein intake[9]. Certainly, cystatin C use has some limitations as a marker of kidney function because it can vary among patients with thyroid disease or on corticosteroid treatment[6,8]. Because of the above-mentioned properties some investigators have focused on the possibility of calculating fracture risk in patients with CKD by measuring cystatin C values with accuracy possibly superior to that of creatinine use.

Cystatin C and the risk of hip fracture in the elderly

When searching the recent literature, we found various publications concentrated on examining whether estimated GFR using cystatin C ($eGFR_{cys}$) is superior to eGFR using creatinine ($eGFR_{cr}$) in predicting the risk for hip fracture in the elderly.

In a study of Fried et al. in 2007 which included 4699 candidates of >65 years of age without fracture, creatinine and cystatin C were measured. The follow up was 7 years and new fractures were recorded. Higher cystatin C was associated with 26% and 27% higher risk of hip fracture in

women and men respectively. When other risk factors were included (age, race, BMI) this result attenuated but remained statistically significant for women (HR 1.16; 95% CI 1.01 to 1.33) but not men (HR 1.14; 95% CI 0.86 to 1.52)[21].

Ensrud et al. in a case-cohort analysis in 2013 showed that cystatin C was a reliable marker to indicate older women who were at higher risk of hip fractures, and more, independently of classic and possibly confounding risk factors such as age or hip bone mineral density (BMD). Of note, no such association could be made with serum creatinine alone or eGFR measurement based on serum creatinine. These results were repeated in women with higher $eGFR_{cr}$ levels ($eGFR_{cr}$>60 ml/min/1.73 m^2), leading to the conclusion that higher cystatin C, even with normal serum creatinine may identify patients in preclinical renal disease[22]. Moreover, in 2012 the case- control study of Ensrud et al. among 93,673 postmenopausal women of all races concluded that White subjects with lower $eGFR_{cys-c}$ and higher cystatin C levels were at increased risk for non-vertebral fractures, while reduced renal function may increase fracture risk among Black women, but there was little evidence to support this association among other racial/ethnic groups[23].

McCarthy et al. in a prospective, population-based cohort study in postmenopausal women with a 25-year follow up, serum creatinine measurement did not predict fracture risk better than traditional risk factors, probably due to the low muscle mass (thus low serum creatinine) in the study group. On the other hand, the authors note that the use of cystatin C increased the accuracy of hip fracture prediction, although cystatin C is a marker of inflammation that could relate to fracture risk independently of GFR[24].

Interestingly, Ensrud et al. in 2014 presented data from research in an older male population that show superiority of cystatin C as well. The higer risk of hip fracture was confirmed for eGFR<60 ml/min/1.73m^2 versus eGFR>75 ml/min/1.73m^2 only for cystatin C (HRs 1.96 95% CI 1.25-3.09, 0.84 95% CI 0.52-1.37, and 1.08 95% CI 0.66-1.77 for $eGFR_{cys}$, $eGFR_{cr}$, and $eGFR_{cr-cys}$ respectively). This relation remained even when risk factors such as age and race were included[25].

In addition, cystatin C -based eGFR measured by CKD-EPI equation seems to be better for osteopenia prediction than creatinine[26], and superior to creatinine in evaluating frailty status (with known consequences in the incidence of fractures in the elderly)[27].

In a study published by Hart et al. including elder male population, cystatin C had 7 times higher odds for frailty (OR 4th quartile vs. 1st 7.12, 95% CI 3.76-13.46). This relation was not confirmed for creatinine[27].

A recently published study in Korean adults concluded that cystatin C might identify women with osteoporosis at higher risk of fractures[28].

Apart from being a marker of renal function, cystatin C has been shown to have other functions that may relate to fractures as well. The basic concept is that CKD is an inflammatory state itself, characterized by high levels of proinflammatory cytokines and homocysteine[22]. In the same line, the possible effect of the TNF-a pro-inflammatory cytokine is mentioned by several studies as a mediator implicated between decline in renal function and fractures[23]. This could be due to the fact that pro-inflammatory cytokines have been shown to increase the expression of Receptor Activated Nuclear Factor-kB ligand (RANKL) and decrease osteoprotegerin (OPG) leading to osteoclast activation and bone resorption[29]. Of interest, according to a cross-sectional study in 8058 inhabitants of the city of Groningen, The Netherlands, 28 to 75 years of age (Knight et al., 2004), there is a positive correlation between Cystatin C and C-reactive protein (CRP) indicating that Cystatin C may increase in inflammatory states independently from renal function status[30].

Moreover, some older research has commented on cystatin C produced by bone cells and its role in bone resorption[31] via its effect on decreasing osteoclast formation[32]. More importantly, higher cystatin C has been directly linked to sarcopenia[33] and consequently to an increase in the number of falls in the elderly[34], reflecting the relationship between declining renal function and loss in muscle mass[35]. These extra mechanisms that implicate cystatin C may be the reason why it is more accurate than creatinine in predicting fractures in CKD patients.

Cystatin C and other complications

Apart from the higher incidence of fractures, patients with higher cystatin C levels are at greater risk for complications such as cardiovascular events and heart failure[36]. Moreover it has been associated with higher mortality risk, risk of stroke and peripheral artery disease, cognitive impairment and impaired physical function related to impaired renal function even at early CKD stages[37]. Lower cystatin C is associated with good mobility in women and could be used as a biomarker of the so-called "successful aging"[7,37].

As a conclusion, according to the above-mentioned observations, cystatin C seems to play an important role as a marker of vascular and other complications accompanying CKD.

Discussion

In this mini review we focused on the recent literature on Cystatin C, as a possible useful tool for assessing eGFR at the time to estimate hip fracture risk in the elderly. Serum creatinine, the most commonly used biomarker in this context in every-day clinical practice, depends on age, diet and muscle mass. On the other hand, cystatin C is independent of these factors but may be influenced by fat mass[38], smoking, male gender, height, CRP[30], corticosteroid therapy and thyroid function[6,8]. Moreover, cystatin C does not overestimate eGFR in the elderly where low muscle mass is profound. The $eGFR_{cys}$ equation can detect patients with milder stages of CKD, otherwise unrecognized and untreated

and sarcopenic patients with CKD, as this populations are at higher risk for fractures too. We believe that there is enough evidence to indicate the better correlation between cystatin C measurement and risk of hip fracture than that of creatinine. Additionally, cystatin C is a better biomarker for other CKD complications such as cardiovascular events. Although we found a superiority of cystatin C in the prediction of fractures, research is concentrated mostly on postmenopausal women. We think that an interesting field of future investigation could be the intriguing idea to use cystatin C in other study groups as well. Moreover, the use of cystatin C is more expensive than that of creatinine, with the cost of a serum cystatin C assay being 12 times as expensive as that of creatinine assay[10].

Conclusion

According to recent studies cystatin C can be used as a biomarker of hip fracture risk in the elderly. Further investigation is needed in order to extract safe results for the use of cystatin C in clinical practice for the prediction of hip fractures, as well as studies on the cost-effectiveness of this method. Future research should also concentrate on the correlation between cystatin C and all fracture types, not only in postmenopausal women but also in men and younger adults.

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