The cystatin C/creatinine ratio, a marker of glomerular filtration quality: associated factors, reference intervals, and prediction of morbidity and mortality in healthy seniors

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The ratio of cystatin C (cysC) to creatinine (crea) is regarded as a marker of glomerular filtration quality associated with cardiovascular morbidities. We sought to determine reference intervals for serum cysC-crea ratio in seniors. Furthermore, we sought to determine whether other low–molecular weight molecules exhibit a similar behavior in individuals with altered glomerular filtration quality. Finally, we investigated associations with adverse outcomes. A total of 1382 subjectively healthy Swiss volunteers aged 60 years or older were enrolled in the study. Reference intervals were calculated according to Clinical & Laboratory Standards Institute (CLSI) guideline EP28-A3c. After a baseline exam, a 4-year follow-up survey recorded information about overall morbidity and mortality. The cysC-crea ratio (mean 0.0124 ± 0.0026 mg/μmol) was significantly higher in women and increased progressively with age. Other associated factors were hemoglobin A1c, mean arterial pressure, and C-reactive protein ($P < 0.05$ for all). Participants exhibiting shrunken pore syndrome had significantly higher ratios of 3.5–66.5 kDa molecules (brain natriuretic peptide, parathyroid hormone, β_2-microglobulin, cystatin C, retinol-binding protein, thyroid-stimulating hormone, α_1-acid glycoprotein, lipase, amylase, prealbumin, and albumin) and creatinine. There was no such difference in the ratios of very low–molecular weight molecules (urea, uric acid) to creatinine or in the ratios of molecules larger than 66.5 kDa (transferrin, haptoglobin) to creatinine. The cysC-crea ratio was significantly predictive of mortality and subjective overall morbidity at follow-up in logistic regression models adjusting for several factors. The cysC-crea ratio exhibits age- and sex-specific reference intervals in seniors. In conclusion, the cysC-crea ratio may indicate the relative retention of biologically active low–molecular weight compounds and can independently predict the risk for overall mortality and morbidity in the elderly. (Translational Research 2016;169:80–90)

Abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CAPA = Caucasian, asian, pediatric and adult cohort; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CLSI = Clinical & Laboratory Standards Institute; Crea = creatinine; CysC = cystatin C; GFR = glomerular filtration rate; HDL = high density lipoprotein; IDMS

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= isotope dilution mass spectrometry; LDL = low density lipoprotein; LM = Lund-Malmö; PTH = parathyroid hormone; SPS = shrunken pore syndrome; TSH = thyroid-stimulating hormone

AT A GLANCE COMMENTARY

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Background

The cystatin C/creatinine ratio has been suggested to capture alterations in glomerular filtration quality. Such changes occur due to the shrinking of glomerular pores, which leaves filtration of very small molecules such as creatinine unimpeded, whereas low–molecular weight proteins are retained in circulation because of their diameter.

Translational Significance

Not only renal function markers but also hormonally active proteins known to be associated with mortality are selectively retained in a disorder called ''shrunken pore syndrome''. An alteration in glomerular filtration quality represents an independent risk factor for morbidity and mortality. The reference intervals for the cystatin C/creatinine ratio reported in this article will allow for a potential clinical use of the investigated ratio.

INTRODUCTION

The human body clears the blood of substances 66 kDa and smaller by glomerular filtration. The structure of the glomerular filtration barrier is complex, and there is no generally accepted 3-D model available.[1] Creatinine is the most readily used endogenous marker for estimating the glomerular filtration rate (GFR), but serum creatinine is influenced by a number of nonrenal factors, such as age, sex, muscle mass, and diet.[2-4] Creatinine is a 113 Da breakdown product of creatine phosphate in muscle and is produced at a fairly constant rate; it is freely filtered across the glomerular membrane, actively secreted in tubules, and is not reabsorbed.[5] When GFR decreases, the tubular secretion of creatinine increases; therefore, a mild degree of kidney dysfunction (<50% reduction in GFR) will not increase the serum creatinine concentration above the upper limit of normal values.[6]

Compared with creatinine, cystatin C is better correlated with GFR and is a more accurate predictor of several clinical outcomes.[7-9] Cystatin C is a 13.3 kDa cysteine protease inhibitor produced by all nucleated cells.[10] It is freely filtered across the glomerular membrane, reabsorbed, and catabolized by the tubules.[11-13] The serum level of cystatin C is also influenced by nonrenal factors, such as steroid medication and thyroid dysfunction.[14,15] However, the cystatin C concentration is considered a better predictor of adverse outcomes compared with directly measured GFR, and this may be because these nonrenal influences enable a superior estimate of actual kidney function.[16]

Because the levels of the 2 markers are affected by different nonrenal factors, their ratio varies. The ratio of cystatin C and creatinine in serum (cysC-crea ratio) is substantially increased in a condition called "shrunken pore syndrome", which is characterized by very different GFR estimates based on the 2 markers ($eGFR_{Cys} \leq 60\%\ eGFR_{Crea}$).[1] Shrinking of the glomerular pores is thought to occur in certain conditions, for example, pregnancy, and is particularly pronounced in cases of preeclampsia.[1,17] Although GFR initially remains normal (and even increases in normal pregnancy), the composition of the glomerular filtrate changes because larger molecules can no longer pass through the pores.[18] Consequently, the serum concentrations of larger molecules increase. Because cystatin C is larger than creatinine, its plasma levels begin to increase first.[19,20] Therefore, an increased cysC-crea ratio indicates a change in glomerular filtration quality that suggests early-stage kidney dysfunction.

The present work aimed to define factors associated with the cysC-crea ratio. We also evaluated reference intervals for this ratio in the elderly. Furthermore, we aimed to explore whether other low–molecular weight molecules display a similar behavior to cystatin C relative to creatinine. Finally, we investigated the cysC-crea ratio as a predictor of morbidity and mortality in healthy elderly individuals.

METHODS

Study population. The present study was conducted within the framework of the SENIORLAB study, the primary aim of which is to establish reference intervals for several laboratory parameters for the elderly (www.seniorlabor.ch). The study consecutively enrolled subjectively healthy elderly volunteers from May 2009 to December 2011. Potential study participants were contacted through newspaper advertisements, various associations with high proportions of healthy