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Can cystatin C-based estimated glomerular filtration rate help to guide individualized risk factor modification programs?

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Editorial

Chronic kidney disease (CKD) is associated with increased incidence and prevalence of cardiovascular diseases and a low glomerular filtration rate (GFR) increases the risk of mortality and cardiovascular complications [1]. Multiple cardiovascular risk factors, direct CKD-related hypervolemia, electrolyte disturbances, acidosis and anemia contribute to the increased cardiovascular risk and mortality in CKD patients. CKD also associates with a hyper-inflammatory state, which may promote cardiovascular remodeling by activation of the inflammasome [2]. Moreover, cardiac and renal norepinephrine spillover is increased in mild-to-moderate and severe chronic heart failure (HF), with absolute renal norepinephrine spillover being higher than the cardiac spillover, suggesting that kidney contributes stronger to total norepinephrine spillover than the heart in HF [3]. Sympathetic activity increases in early CKD phases, with magnitude of sympathetic overdrive increasing with disease progression [4,5]. In the setting of atrial fibrillation, CKD-related factors may promote the progression of atrial remodeling, creating a substrate that may lead to atrial fibrillation in response to increased cytokine surges (e.g. cardiac surgery) or hypoxemic episodes (e.g. sleep apnea) [6,7].

Clinically, renal function is assessed by the estimated glomerular filtration rate (eGFR) routinely calculated by the MDRD Study and the (CKD-EPI) equations which include the plasma creatinine concentration, gender, race and age as variables. The plasma creatinine concentration does not only depend on the kidney clearance function but is also affected by muscle mass and the intensity of physical activity during the previous days, potentially underestimating the renal function in subjects undergoing physical exercise. An alternative strategy to determine renal function is the cystatin C-based eGFR. Cystatin C is a single-chain protein produced by all nucleated human cells and distributed in extracellular fluid. It is freely filtered and mostly reabsorbed and catabolized by the proximal tubule. Cystatin C is not affected by muscle mass, physical exercise or diet and is less strongly associated with age, sex, and race than creatinine, although smoking, inflammation, adiposity, thyroid diseases, malignancy, and glucocorticoids influence cystatin C levels.

Cystatin C-based eGFR appears superior to creatine-based eGFR in different patient cohorts. Among 3557 participants in the CRIC Study, cystatin C-based eGFR and albuminuria were better predictors for HF risk compared to creatinine-based eGFR [8]. Cystatin C-based glomerular filtration rate associates more closely with mortality, hypertension and the renal resistance index than creatinine-based or combined glomerular filtration rate equations. Although, the prognostic value of eGFR during targeted therapeutic interventions is unclear, it might help to guide interventions such as comprehensive cardiac rehabilitation programs and other risk factor modification programs.

In this issue of the IJCHV, Hama et al. [9] validated the effect of cardiac rehabilitation on the eGFR using cystatin C. They included 86 patients with a lower-moderate CKD who participated in their 3-month cardiac rehabilitation program. At 3-months of cardiac rehabilitation program, the exercise capacity assessed by peak oxygen uptake and peak work rate increased, in association with improved cystatin C-based eGFR, but not creatinine-based eGFR, pointing to a favorable effect of their cardiac rehabilitation program on renal function when assessed with cystatin C-based eGFR only. Lines of evidence suggest that cystatin C-based eGFR and circulating cystatin C level represent helpful risk markers to estimate cardiovascular and mortality risk and may help to detect early subclinical target organ damage in some patients. Hama et al. [9] showed that their cardiac rehabilitation program favorably modifies renal function assessed by cystatin C-based eGFR, although it is unknown whether this also translates into a reduction in cardiovascular risk and a better outcome. A Mendelian randomization analyses did not support a causal role of cystatin C in the etiology of

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cardiovascular disease questioning the possibility that cystatin C is a modifiable cardiovascular risk factor [10]. Thus, therapeutic targeting to lower the levels of circulating cystatin C is not expected to prevent cardiovascular diseases [10].

In conclusion, although cystatin C-based eGFR may represent a helpful biomarker to monitor and guide interventions thereby estimating their impact on cardiovascular risk, the clinical benefit of considering cystatin C as a biomarker require further validation. Particularly the additive benefit of cystatin C-based eGFR as a new biomarker on top of established markers and risk models is currently unknown. Whether cystatin C can help to guide individualized early initiation of treatment and risk factor management needs to be investigated in subsequent studies. Future research should also dissect whether cystatin C-based eGFR improves risk assessment in the general publication or just in certain populations such as CKD and heart failure. Whether its reduction constitutes a treatment target or whether its reduction goes hand in hand with cardiovascular risk reduction and can be used to guide individualized risk factor modification and cardiac rehabilitation programs warrants further prospective and randomized large-scale studies.

Conflict of interest

None (all authors).

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