In Focus

It’s not only the kidneys—genetic determinants of glomerular filtration marker levels

Carsten A. Böger

Correspondence and offprint requests to: Carsten A. Böger; E-mail: carsten.boeger@klinik.uni-regensburg.de

The estimated glomerular filtration rate (eGFR) and albuminuria are the two key measures of kidney function used to classify chronic kidney disease (CKD) due to their ease of determination from blood and urine samples. Since Rehberg’s studies of 'filtration and reabsorption in the human kidney' almost 100 years ago [1], sophisticated GFR estimation equations have been developed for routine medical care [2, 3]. These formulae rely heavily on serum creatinine. However, creatinine is an imperfect filtration biomarker since it is dependent on age, muscle mass and meat consumption, and is actively secreted by the kidney tubules, especially when kidney function declines. The creatinine-based formulae show significant imprecision in the normal range of GFR, frequently leading to misclassification. These drawbacks of creatinine have spurred the search for novel filtration biomarkers. Beta-trace protein (BTP), cystatin C and beta-2-microglobulin (B2M) have emerged as promising candidates to replace creatinine since they are independent of muscle mass, freely filtered by the glomerulus, then catabolized and/or excreted, but not secreted by the kidney tubules [3]. These novel filtration markers have significant limitations that need consideration in their process of validation: B2M is increased in malignancy and inflammation and excreted under conditions of tubular dysfunction, and cystatin C and BTP are affected by steroid therapy. Expression of BTP, also known as lipocalin-type PGD(2) synthase (L-PGDS), is increased in certain inflammatory states [4, 5], and L-PGDS/BTP expressed in the kidney may promote the development of CKD by production of prostaglandin D(2) and subsequent activation of Th2-lymphocytes [6]. Complicating matters, L-PGDS/BTP is a potential marker of kidney injury in type-2 diabetes [7]. Finally, international standardization of the assays of these markers has only recently been established for cystatin C [8].

In this edition of NDT, Tin et al. [9] now present a further important non-renal determinant of BTP concentrations: genetic variation. In a genome-wide association study (GWAS) on 6720 European Americans (EAs) of the general population in the ARIC study, single nucleotide polymorphisms (SNPs) at the locus containing the gene coding for BTP, prostaglandin D2 synthase (PTGDS), were significantly associated with BTP levels. The index SNP at the locus explained 1.1% of the variance of log(BTP) levels, and the index SNP’s effect allele was responsible for 5% higher BTP levels in EAs compared with the reference allele. Unfortunately, though BTP-based GFR estimation equations have been developed for transplant, Fabry and paediatric patients [10–12], no such formula is available for general population cohorts to determine the absolute difference in the eGFR attributable to the SNP. However, though this SNP’s effect size is large for the GWAS, the absolute eGFR difference due to the SNP will likely be of low clinical relevance.

The PTGDS locus was validated in genetic association analysis in 1734 African Americans of the ARIC study, with a similar effect of the index SNP on BTP levels as in EAs. Interestingly, over a third of the difference of log(BTP) levels observed between the two ethnicities could be ascribed to the index SNP at the locus. The absolute difference in median BTP levels between ethnicities was only 0.09 mg/L, but this 15% difference is larger than the 4–7% difference in serum creatinine between Africans and Caucasians in NHANES [13]. Since it is unlikely that other factors such as inflammation play a major role in determining between-ethnicity differences of BTP, this finding suggests that genetic testing may become an important alternative to potentially inaccurate self-reported ethnicity when using GFR-estimating formulae.

The index SNP was not associated with eGFR or albuminuria in either ethnicity in ARIC, indicating that the SNP affects BTP levels by modifying production or metabolism but not

Department of Internal Medicine II, Nephrology, University Medical Centre Regensburg, 93042 Regensburg, Germany

Keywords: beta-trace protein, chronic kidney disease, genome-wide association studies, GFR estimation equations, glomerular filtration markers
kidney function. BTP levels do show association with SNPs previously identified by a large GWAS meta-analysis of eGFR [14, 15], in support of BTP’s known correlation with serum creatinine [16] and potential role as a novel filtration marker.

Genetic variation is known to affect the levels of other filtration markers via non-renal effects on production, metabolism and secretion: SNPs identified by GWAS meta-analysis in the CKDGen consortium in several genes including GATM and SLC22A1 influence serum creatinine levels, and SNPs in the CST gene cluster affect cystatin C levels [14, 15]. Importantly, these SNPs are distinct to over 20 additional SNPs associated with true kidney function in GWAS meta-analysis, explaining a small fraction of the 36–75% of total heritability of true kidney function [17].

Taken together, the GWAS by Tin et al. [9] and the CKDGen Consortium [14, 15] are important contributions to elucidating the role of genetic variation in determining filtration biomarker levels. A future perspective for the development of GFR estimation equations based on novel biomarkers could be the incorporation of genetic information relevant to the used filtration marker. In the case of BTP, the influence of inflammation on biomarker levels and BTP’s role in CKD pathogenesis need to be clarified, and the molecular mechanisms leading to altered biomarker levels need to be unravelled to determine the true functional SNPs. Further genetic studies are needed to determine the effect size of the causative SNP in the context of populations of different ethnicities and disease background. The perspective of a novel GFR estimation equation with a genetic component will certainly only become reality if inclusion of genetic information is shown to improve precision and reduce bias in GFR estimation significantly. This is especially important, given the added cost and ethical caveats that come with routine genetic testing.

ACKNOWLEDGEMENTS

CAB has received research funding from the Else Kröner-Fresenius-Stiftung, the Dr Robert Pfleger Stiftung and the KfH Stiftung Präventivmedizin.

CONFLICT OF INTEREST STATEMENT

None declared. The material in this paper has not been published previously in whole or part.


REFERENCES


Received for publication: 5.1.2013; Accepted in revised form: 26.2.2013