

Disparate CKD associated outcomes in South Asians- ethnicity or eGFR?

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Chronic kidney disease (CKD) is currently ranked at 16th place in the list of global years of lives lost by the Global Burden of Disease Study, and is projected to rise to rank 5 by the year 2040. This increase is faster in some parts of the world compared to others. (1) Contrary to the usual perception of its inevitable progression to end stage kidney failure, a substantial proportion of patients with CKD die of cardiovascular (CV) complications in earlier stages of disease. A remarkable body of work - led by the Chronic Kidney Disease Prognosis Consortium (CKD-PC) and the CKD Epidemiology Collaboration, and using data from cohorts from around the world- has confirmed the relationship between common markers of kidney disease and the development of cardiovascular disease (CVD) and all cause as well as CV mortality.(2) Both estimated glomerular filtration rate (eGFR) and albuminuria have independent as well as multiplicative impact on outcomes. These findings have been shown to be consistent in several populations around the world. Interestingly, there is no data so far on these association in South Asians, especially from India.

The Baseline Southall and Brent studies were set up in 1988-91 to study the balance between genetic and environmental influences amongst migrants to UK of South Asian (mostly Indian) and Afro-Caribbean origins and the native UK population of European origin.

In this issue of the Journal, Eastwood et al report their findings on the association between kidney function markers (eGFR and urinary albumin-creatinine ratio [ACR]) at baseline and incident CVD and mortality after 20 years and examine the ethnicity-specific differences between Indo-Asians and Europeans from Southall in this cohort(3). About 30-40% of invited participants had declined to be enrolled in the original baseline study. The age at the time of recruitment was 40-69 years. Of the 3754 participants from Southall, the current analysis included 2220 participants (Indo-Asians: 1104, Europeans: 1116). eGFR and ACR were measured only at baseline. Outcome data were collected by linkage with NHS Digital that allowed ascertainment of deaths and CVD episodes, showing the value of data linkage.(4)

The two ethnicities exhibited important baseline differences related to CV risk: South Asians had more adverse CV risk profile, including lower eGFR_{crea} and ACR values. Of note, when participants placed under a certain CKD stage on the basis of eGFR_{crea} were reclassified

based on eGFR_{cys} values, South Asians were more likely to be designated to a more adverse CKD stage. The authors found both eGFR_{cys} and eGFR_{creat} to be associated with mortality and incident CVD in Europeans. However, this association was absent for eGFR_{creat} and eGFR_{cys} in South Asians. In contrast, ACR was more strongly associated with outcomes in South Asians than Europeans. This finding was confirmed using several modelling approaches.

The study supports the narrative on the ethnic differences in biological behavior of diseases. Prima facie, it would seem that pathophysiology of CKD and its complications may be different in the two ethnic groups and may suggest the need to adopt a differential approach to assessment and management of CKD depending on ethnicity. A faster progression of CKD and higher albuminuria has been reported in South Asians and other ethnic groups in comparison to Caucasians.(5)

However, a deeper look into the results and application of principles of biological plausibility is warranted. The authors have postulated eGFR and albuminuria as complimentary markers of kidney function, with albuminuria indicating the particular susceptibility of South Asians to microvascular disease and endothelial dysfunction. A differential impact of eGFR and albuminuria on CVD and mortality has been shown in the CKD-PC analyses. (2) eGFR shows a threshold effect, with the risk rising after $\text{eGFR} < 70 \text{ ml/min/1.73 m}^2$, whereas albuminuria has a continuous gradient of increasing risk starting from very low levels, even below the current definitions of microalbuminuria. Studies have shown that differences in the albumin excretion rates between individuals become evident at a very early age after birth and persist for decades suggesting a pre-defined state of endothelial/renal health.(6) This 'level of endowment' of albuminuria also may indicate the variations in propensity to development of conditions like diabetes, hypertension, CV disease later in life.

Since the eGFR did not predict outcomes as expected in South Asians, we should examine the issue of ethnicity-specific differences in GFR estimation. The equations the authors used for South Asians have been derived primarily in Caucasians, and are shown to be imprecise for in many populations. The 2002 KDOQI guidelines lay down a performance measure for accuracy of eGFR equations requiring that the eGFR values derived from such an equation

should be within 30% of the measured GFR obtained using a gold standard method in >90% of the participants ($P_{30}>90\%$). A recent study from India showed the P_{30} for eGFR_{creat} (CKD-EPI) to be just 22%. eGFR_{cys}, which corrects for fallacies of creatinine-based equations, performed better at 75%, but still fell short of the desired P_{30} .⁽⁷⁾ The CKD-EPI_{creat} equation consistently overestimated the true GFR, which could explain the reclassification to a more adverse category in South Asians when eGFR_{cys} was used, and also the inability of the creatinine-based equations to accurately predict outcomes. The reasons of the poor performance of creatinine-based equations could be related to the lower muscle mass, different body habitus and vegetarian dietary habits in South Asians.

The exact causal pathways linking CKD to CVD have not been established, but a plethora of mechanisms have been proposed. Given the strong evidence from several population groups, such relationship is likely to be present in South Asians as well. Perhaps development of a more accurate ethnicity-specific equation, as has been done for Chinese, Japanese, Korean and Thai populations, will unmask the predictive value of eGFR for clinically important outcomes in South Asians. It is important to answer this question, so as to appropriately tailor the high-risk group approach for health care interventions and advocacy for funding for population segments. The ongoing Indian Chronic Kidney Disease Study ⁽⁷⁾ may help shed light on this.

Can such findings be explained simply on the basis of genetic differences? The human genome project educational material stated “two random individuals from any one group are almost as different [genetically] as any two random individuals from the entire world.” Further, when individuals are sampled homogeneously from around the globe and not pre-selected based on particular regions or predefined attributes, the patterns of allele frequencies show a gradient across the world rather than presence of discrete clusters. ⁽⁸⁾ Further studies are required to explore the interplay between genetic and non-genetic differences that have accumulated over millenia in different population groups and might be responsible for these biological differences. This understanding is important for developing future personalised medicine approaches.

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