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Impaired Renal Function and Cerebrovascular Disease

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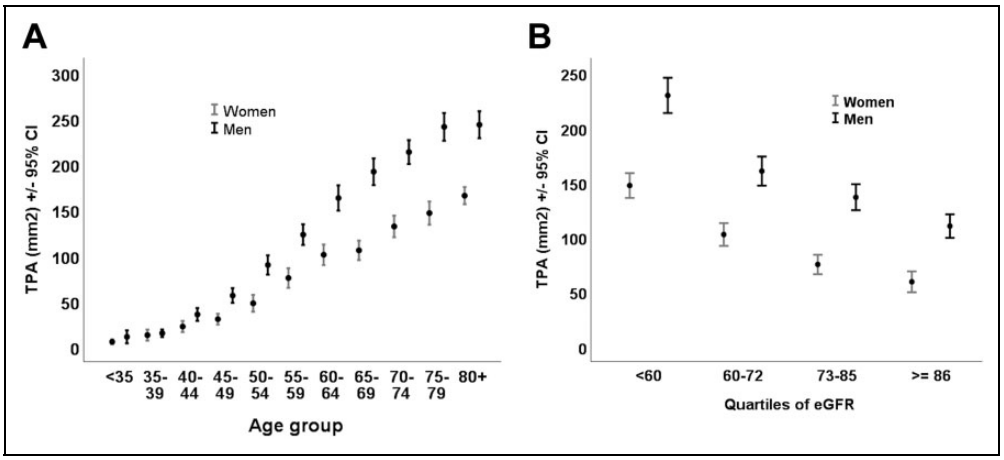

Figure 1. Carotid total plaque area (TPA) by age-group and quartile of estimated glomerular filtration rate (eGFR) Among patients attending the Stroke Prevention & Atherosclerosis Research Centre, London, Canada (n = 3977), TPA increases steeply with age (A), and with impaired renal function (B); eGFR (mL/min/1.73 m^2) was calculated by the chronic kidney disease (CKD)-Epi equations. At any age, and at any level of renal function, women have less plaque than men. (The figures have not previously been published; they were drawn from the database of a previous study).[7]

In this issue of *Angiology*, Puvvula et al[1] report that both carotid intima-media thickness (IMT) and carotid plaque burden, measured as total plaque area (TPA), were increased in patients with impaired renal function, assessed as estimated glomerular filtration rate (eGFR). A recent editorial in this journal explained why measuring plaque burden is superior to measuring IMT, which is biologically and genetically distinct from atherosclerosis, and can be regarded as obsolete technology.[2] Puvvula et al studied 678 participants with a mean age of only 54.2 ± 9.8 years, so they observed relatively small effects of renal impairment on IMT and atherosclerosis. Total plaque area increases steeply with age (Figure 1A), so effects of impaired renal function are more evident among older patients. Figure 1B shows TPA by quartiles of eGFR among patients (n = 3967) aged 62.6 ± 13.7 years, attending the Stroke Prevention and Atherosclerosis Research Centre, in London, Canada.

This is not a new observation; it has been known for many years that impaired renal function markedly increases cardiovascular risk[3] and increases atherosclerosis burden, particularly in diabetic patients.[4] Renal failure also increases the risk of stroke[5] and cerebral microbleeds.[6] What is new is a better understanding of the mechanisms by which renal failure increases risk of stroke and coronary artery disease and aggravates atherosclerosis. Patients with chronic kidney disease (CKD) have high plasma levels of phosphates, asymmetric dimethylarginine (a nitric oxide antagonist), and total homocysteine (tHcy); however, tHcy probably only accounts for ~20% of the excess plaque related to impaired renal function.[7] Levels of thiocyanate, a powerful oxidant,[8] are high in renal failure and excretion of cyanide as thiocyanate probably

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consumes hydrogen sulfide (H_2S), an endothelium-derived relaxing factor.[9]

An important development in this field is the understanding that patients with CKD also have very high plasma levels of toxic metabolites produced by the intestinal microbiome. Perhaps the best known is trimethylamine *N*-oxide (TMAO), produced largely from phosphatidylcholine in egg yolk and carnitine in red meat ($\sim$4 times as much in red meat as in white meat). High levels of TMAO markedly increased cardiovascular risk among patients referred for coronary angiography; patients with TMAO levels in the top quartile had a 2.5-fold increase in the 3-year risk of myocardial infarction, stroke, or vascular death.[10] Among persons with CKD, TMAO accelerated the decline of renal function and increased mortality.[11]

Besides TMAO, a number of other toxic metabolites are produced by the intestinal microbiome from amino acids consumed in protein. Among persons with severe atherosclerosis not explained by traditional risk factors ("Unexplained atherosclerosis"), plasma levels of TMAO, p-cresylsulfate, p-cresylglucuronide, and phenylacetylglutamine were significantly higher than in those who had little or no plaque despite high levels of risk factors (a "Protected" phenotype). There were not significant differences in diet or renal function across phenotypes, so the differences in plasma levels of metabolites are probably due to differences in the intestinal microbiome. In linear regression, both TMAO and p-cresylsulfate were significant predictors of TPA.[12] With funding from the Canadian Institutes of Health Research, our team will soon initiate a clinical trial of repopulation of the intestinal microbiome in patients with unexplained atherosclerosis, replacing their intestinal bacteria with donor stool from patients with the "Protected" phenotype.[12] The objective is to determine which intestinal bacteria are associated with a reduction in plasma levels of toxic metabolites, to permit design of an "ecosystem therapeutic" of cultured bacteria, as has been done for the treatment of infection with *Clostridium difficile*.

Although it was known that patients with severe renal failure had very high levels of such toxic products of the intestinal microbiome (50- to 100-fold higher than in those with normal renal function), it recently became apparent that plasma levels of all 7 metabolites measured in one study (TMAO, p-cresylsulfate, hippuric acid, indoxyl sulfate, p-cresylglucuronide, phenylacetylglutamine, and phenyl sulfate) were elevated with even moderate impairment of renal function, to an eGFR <66 mL/min/1.73 m^2.[13] Renal function declines linearly with age, and the average eGFR reaches 66 mL/min/1.73 m^2 by the age of 75,[7] so this information has important dietary implications. Notwithstanding a recent paper in this journal by Takagi et al,[14] dietary cholesterol and egg consumption do increase cardiovascular risk.[15] For patients with impaired renal function, including the elderly, it is important to avoid egg yolk and limit meat consumption.

Declaration of Conflicting Interests

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