Why do older people get so much kidney disease?

To celebrate Sir William Osler's 70th Birthday on July 12th 1919 his pupils and co-workers contributed scientific articles that were collected and published. One of these articles, by William Councilman pathologist-in-chief at Peter Bent Brigham Hospital, noted that there "are few conditions which so generally repeat themselves as does that of the kidney in old age…… (the changes) are as characteristic of age as is the shrunken shank and tottering gait". Over the subsequent almost 100 years much controversy has swirled around the realization that kidney disease causes high blood pressure and that high blood pressure causes kidney disease. The "chicken or egg comes first" argument has waxed and waned, but the pragmatic outcome has been that treatment of high blood pressure remarkably preserves kidney function. With the advent of publically funded dialysis treatment for (end stage) kidney failure has come government-mandated reporting of both the costs of kidney failure to society (7% of Medicare funds at more than $40billion per year) and epidemiologic reporting to discover who actually gets kidney failure. It turns out that although all groups get kidney failure with devastating consequences to individuals and their families, in terms of numbers it is older people who are by far the major target. Being more than 60 years old carries more than twice the risk of kidney failure compared to diabetes and hypertension, previously thought to be the major "causes". So the scientific question is an apparently simple one. Why do older people get more kidney failure?

Enormous advances have been made in the science of aging. Molecular pathways related to insulin-signaling have been discovered to play key roles in the longevity of worms, flies and mice. Dietary calorie reduction reliably prolongs lifespan through this pathway. However, it is not entirely clear how these discoveries can be translated into human longevity, and in particular how they impact life-threatening diseases affecting complex organs of the body such as heart or kidney. Humans live on average for more than 80 years, so the impact of underlying genetic predispositions has a long time to become interwoven with superimposed environmental factors, just as a lifetime of smoking causes lung cancer in some people but not others.

The kidney's job is to maintain the "purity" of the body by getting rid of waste products while retaining useful components from the diet. It achieves this by a two-step process. First the blood is filtered by a "glomerulus". The glomerular filtrate then flows down a tube (the "tubule") which has various regions that each do specialized tasks of reclaiming or rejecting what the body needs or does not need under the control of feedback loops and hormones supplied by brain, heart and adrenal glands that sense the overall balance of the body's metabolism.

Our story concerns the glomerulus, the sieve-like filtering structure made up of specialized blood vessels whose inner lining of endothelial cells cover a membrane supported by specialized cells called podocytes because they has thousands of feet (pods). These pods maintain the filter while at the same time permitting the filtrate to pass through a molecular sieve that retains larger structures such as proteins but allows smaller components such as water, ions and small molecules through. Podocytes, like neurons, are long-lived cells with limited capacity for

replacement after birth. Collectively they are tasked to cover the entire filtration surface with their feet for the filter to function normally. Failure to do this results in leakage of protein from blood into the filtrate. This leakiness is called proteinuria (protein in the urine) which, if severe, results in fluid retention and swelling of the tissues (the Nephrotic Syndrome).

Over the last 20 years it has become clear that podocyte damage and loss is the major cause of glomerular scarring that accounts for more than 80% of all kidney failure. This important scientific advance is based on work in animal models, genetic analysis of children with nephrotic syndrome, and kidney biopsies from people with diabetes, hypertension, FSGS, lupus, IgA nephropathy and other glomerular diseases.

Returning to the question of why old kidneys fail. If podocyte damage and loss causes all glomerular failure, then could the same mechanism be somehow responsible for age-associated kidney failure? The Wiggins laboratory developed quantitative methods to ask this question. They found that podocyte density (number per glomerular volume) does decrease with age to a level known to result in protein leak into the urine and glomerular scarring. They also observed a sequence of events whereby a critical reduction in podocyte density could cause collapse and scarring of the glomerulus as typically seen in old kidneys. This would be analogous to age-associated diseases such as Alzheimer or Parkinson's disease of the brain where loss of other long-lived cells (neurons) eventually results in a critical depletion beyond which brain function becomes noticeably and progressively impaired. Also similar to the dementias, the Wiggins laboratory found that vascular disease of the kidney seems to participate, as has long been suggested. They propose that all progressive glomerular diseases are accelerators of this underlying aging mechanism. If this result can be confirmed by other investigators it will provide an opportunity for new approaches aimed at identifying people at risk for developing kidney failure, applying preventive measures early in life, and being able to monitor efficacy of interventions through urine testing.

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Publication

Podometrics as a Potential Clinical Tool for Glomerular Disease Management.
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