Glomerular Effects of Age and APOL1

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Two articles in this issue of JASN seek to identify structural weaknesses that render glomeruli liable to failure. Hodgin et al.1 examine glomerular loss with aging and propose that a gradual reduction in the number of podocytes per unit glomerular volume reaches a point where it triggers glomerular failure. As glomeruli are lost, compensatory hypertrophy of those that remain leads to additional reduction in podocyte density, because podocytes are terminally differentiated and cannot divide. The resultant self–perpetuating process of glomerular destruction causes age-related loss of renal function.

In advancing their podometric view, Hodgin et al.1 re-examine the problem of age-related loss of renal function at increased structural resolution. However, as noted in the introduction to the work by Hodgin et al.1 and recently reviewed by Glasscock and Rule,2 it has been remarkably hard to characterize even the more basic structural features of renal aging. This difficulty is exemplified by the two JASN papers that we are considering. Hodgin et al.1 report that glomerular volume increases markedly with age. Hoy et al.3 see little change in glomerular volume with age, except perhaps in African Americans with APOL1 risk alleles. Differences in tissue processing and clinical parameters, including body size, may account for some of the variation in these descriptions and others of renal aging. We suspect that differing morphometric methods are also a major source of variation. Hodgin et al.1 calculate average glomerular volume on the basis of the area of open glomerular profiles. Sclerosed glomeruli are not included in the calculation. Hoy et al.3 calculate average glomerular volume as the aggregate volume of glomeruli divided by the number of glomeruli. Inclusion of sclerosed glomeruli will tend to keep the average volume stable if some glomeruli enlarge while others are sclerosed. The magnitude of the difference will be increased by underrepresentation of shrunken glomeruli in small biopsy specimens as opposed to larger autopsy specimens unless mathematical corrections are made. Measurements may also be affected by inclusion of more superficial glomeruli in biopsy specimens.

Recognizing that average glomerular volume is assessed by different methods, we can accept that some glomeruli enlarge while others are lost over the course of a lifetime. We presume that this occurs to varying extents in different people depending on factors, including birth weight, sex, dietary habits, body size, BP, and genetic inheritance, including race. We do not undertake to say that the process is normal, but only that it occurs in our society. Additionally, the extension of a fixed number of podocytes over an enlarged glomerular surface may cause injury because of podocyte insufficiency, which was originally proposed by Fries et al.4 The concept that podocyte insufficiency is central to progressive loss of glomerular function has since received support from studies in both human and animal disease.5 In the work by Hodgin et al.,1 they extend this concept to account for age-related loss of renal function in people without clinical renal disease.

The findings in the work by Hodgin et al.1 are intriguing and will undoubtedly stimulate additional study. One question is why Hodgin et al.1 find glomerular enlargement that is out of proportion to the extent of glomerular loss with age as reflected by the prevalence of sclerosed glomeruli. A possible answer is that sclerosed glomeruli are not only underrepresented in tissue sections because of their small size but also, that, over time, they are resorbed.6 More difficult to explain, if we accept the primacy of podocyte insufficiency in age-related injury, is why aging humans do not exhibit proteinuria and segmental glomerular sclerosis. Proteinuria and segmental sclerosis appear when podocyte loss is induced in animals and have also been considered hallmarks of secondary injury to hypertrophied remnant glomeruli after nephron loss in humans.5 Hodgin et al.1 suggest that glomeruli slowly enlarge to a point where they rapidly fail, and therefore, only small numbers of glomeruli are in the process of failing at any time. Inferences on the basis of protein excretion and GFR decline rates in secondary glomerular sclerosis, however, lead us to expect that age-related loss of renal function should still be accompanied by proteinuria and segmental sclerosis if it were similarly ascribable to podocyte insufficiency.7

Although they do not find segmental sclerosis in aging glomeruli, Hodgin et al.1 do see evidence of mass podocyte detachment events and proteinaceous material in Bowman’s space. These findings may provide new clues to the mechanisms of age–related glomerular loss, and we can hope to see them examined further at still higher resolution. Recent studies have emphasized the role of autophagy, which removes dysfunctional mitochondria and other cytoplasmic.
debris, in determining the lifespan of cells. Autophagy is thought to be particularly important to the long-term survival of terminally differentiated neurons and by analogy, podocytes, which cannot lower their concentration of cytoplasmic debris by division. Reduced autophagy could, thus, cause podocyte loss with aging, even when no additional podocyte stress is imposed by glomerular hypertrophy. If this is the case, we might expect to observe accumulation of dysfunctional mitochondria and other debris in aging podocytes. Such changes have recently been associated with glomerular aging in mice but have not yet documented in humans. Whether such findings can differentiate age–related podocyte injury from other forms of podocyte injury remains to be determined. We should note, in particular, that glomerular injury may be a consequence of tubular injury, and we are not yet sure that the glomerular changes evoked by tubular injury are distinct from those seen with aging. The appealing hypothesis that age-related injury begins with the loss of the long–lived, terminally differentiated, and fantastically ramiﬁed podocyte, thus, provides attractive opportunities for additional study.

The description of age–related structural changes by Hodgin et al provides useful background for the description of structural effects of APOL1 risk alleles by Hoy et al. What do we see when a genetic predisposition to renal insufﬁciency is superimposed on the processes of normal aging? Before the APOL1 risk alleles were identiﬁed, Hughson et al. had looked for features of renal structure that could account for the increased risk of renal failure in African Americans relative to European Americans. In particular, Hughson et al. tested the hypothesis that renal failure in African Americans could be attributed to a lower nephron endowment. Results in nearly 200 autopsy kidneys collected at the University of Mississippi Medical Center from people without known renal disease, however, revealed a tendency toward reduced glomerular number with higher BP but no major ethnic differences.

Hoy et al. describe their additional examination of the University of Mississippi autopsy material in light of knowledge that APOL1 risk alleles are responsible for much of the increased incidence of nondiabetic kidney disease in African Americans. As shown in table 1 in the work by Hoy et al, the genetic proﬁle of the study population was similar to the African-American population at large; therefore, among 159 African-American subjects, 43% had one risk allele, and 19% had two risk alleles. To those seeking a structural explanation for the increased risk of renal failure in African Americans, the results are again largely disappointing. Overall, African Americans with one or two APOL1 risk alleles did not have fewer glomeruli, larger glomeruli, or more glomerular sclerosis or cortical ﬁbrosis than African Americans without risk alleles. This new ﬁnding may be paired with the recent description of biopsies from patients with FSGS with and without APOL1 risk alleles by Kopp et al. Together, the two studies reveal no distinctive structural stigmata of APOL1 risk alleles in people with or without clinical renal disease.

As noted by Hoy et al, more detailed examination still could reveal structural defects associated with APOL1 risk alleles. In particular, there has been speculation that APOL1 risk alleles cause podocyte injury. We may, thus, expect to see studies examining whether APOL1 risk alleles cause the acceleration of the age–related podocyte loss that was described by Hodgin et al or other podocyte abnormalities. Also, the report of Hoy et al, although it does not show an overall diﬀerence in the kidneys of African Americans with and without APOL1 risk alleles, does reveal a potential eﬀect of these alleles on aging. Glomerular number, which Hoy et al. ﬁnd stable from age 20 to 57 years old in non-African Americans and African Americans without risk alleles, seems to decline with age in African Americans with two risk alleles. Analysis of this finding reveals the diﬃculty that the investigators face, which was previously seen in the study by Hodgin et al, in addressing seemingly simple structural questions. We cannot tell what has happened to resorbed glomeruli, and we cannot get tissue samples at will from people with carefully studied renal function. We, thus, cannot be sure that the changes seen in aging in African Americans with risk alleles would not have been seen in other subjects carefully matched for body size and GFR. We know that renal insuﬃciency develops more often and progresses faster in African Americans with risk alleles but cannot yet see how the alleles have hurt the kidney. As with the problem of age-related decline, additional studies will be required to determine where the trouble starts.

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DISCLOSURES

None.

REFERENCES


