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HEALTHY AND UNHEALTHY AGING ON KIDNEY STRUCTURE AND FUNCTION: Human Studies

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Abstract

Purpose of Review: This review is intended to provide an up-to-date analysis of the structural and functional alterations of the kidneys that accompany healthy and unhealthy aging in humans. Macro- and micro- structural changes and glomerular filtration rate (whole kidney and single nephron) accompanying aging will be stressed.

Recent Findings: Comparative findings concerning distribution of anatomic changes of the kidney healthy and unhealthy aging are reviewed. Challenges concerning definition of Chronic Kidney Disease (CKD) in otherwise healthy aging subjects is discussed. The complex interactions of CKD and aging is discussed. The role of podocyte dysbiosis in kidney aging is reviewed.

Summary: Kidney aging is a complex phenomenon often difficult to distinguish from CKD. Nonetheless, phenotypes of healthy and unhealthy aging are evident. Much more information concerning the molecular characteristics of normal kidney aging and its relevance to chronic kidney disease is needed.

Keywords

Aging; Kidney Anatomy; Kidney Function; Glomerular Filtration Rate; Chronic Kidney Disease

INTRODUCTION and SCOPE:

The changes in the structure and function of the kidneys during the process of aging have been studied for many decades (1). The underlying biology of kidney aging remains elusive and likely involves genes, environment and chance (1, 2). We now have an appreciable understanding of the normal kidney aging (3). Animal experimentation in murine species has shed much light on the process of kidney aging (4), but important differences exist between human and murine aging at the descriptive level, so modeling of kidney aging from laboratory animals in forced captivity and a proscribed environment may not be translatable to humans. There are also differences between aging humans that are only indirectly related

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Conflict of Interest

There are no conflicts of interest.

to the aging process *per se*. The kidneys can be affected by co-morbid features, such as obesity, diabetes and hypertension that commonly accompany aging (5). This complicates the analysis of how aging affects kidney structure and function; i.e, what differences exist in the kidneys with "healthy" aging (in the absence of overt co-morbidity) and unhealthy aging. Events in early intrauterine development, such as nephron under-endowment, may set in motion adaptive changes that affect structure and function of the kidneys later in life, even among apparently healthy subjects (6, 7). It is the intent of this review to analyze the processes in both healthy and unhealthy kidney aging in humans and to contrast these findings with those found in aging animals. Molecular studies will not be covered, as this topic has been covered in other recent reviews and original investigations (1, 8–10).

HEATHY AGING IN HUMANS

Structural changes- macroscopic and microscopic

The anatomy of kidney cortex and medulla does not change in parallel with healthy aging. Instead, up to age of 50 years, whereas medullary volume increases, cortex volume declines, providing a false impression that kidney does not change macroscopically with aging (11, 12). Only beyond age of 50 years, when the cortex further atrophies, can a decline in total kidney volume be fully appreciated. This age-related decline in cortex volume (but not medulla volume) has recently been demonstrated using novel deep-learning-based approach in a multicenter study of 1612 potential kidney donors (13).

Another common macroscopic feature of an aging kidney is a higher prevalence, number, and size of benign simple cysts (14). Computerized tomography (CT) studies in potential kidney donors have revealed that focal cortical scars, fibromuscular dysplasia, parenchymal calcifications, atherosclerosis of kidney arteries (15), and kidney surface roughness (16) also increase with older age.

One of the most frequently described micro-anatomical changes in healthy aging is an age-dependent increase in the frequency of focal and global glomerulosclerosis (FGGS). Virtually all studies, including autopsy and studies in living kidney donors, agree that even in the absence of an overt kidney disease, the prevalence of focal and global (but not focal and segmental) glomerulosclerosis increases with older age (17–20). While FGGS increases, the number of healthy/viable glomeruli decreases. A study in living kidney donors ranging from 18 to 75 years of age, demonstrated that nephron loss in the oldest individual can be significantly *underappreciated* by the commonly reported metric of the percent of globally sclerosed glomeruli in kidney biopsies. This may be due to progressive atrophy and eventual reabsorption of globally sclerosed glomeruli (20). Over a 50+ year span of aging about 50% of the original nephron endowment is lost by physiological aging (20, 21). While enumerating nephrons by combinations of volumetric CT scans for cortical volume and kidney biopsy stereology for glomerular density is not precise in individual patients (22), reasonably accurate population-level patterns can be described in large cohorts (20, 23–25). Another interesting aspect of age-related global glomerulosclerosis is that it increases with age primarily in the superficial cortex (Figure 1 and 2), whereas global glomerulosclerosis associated with underlying disease occurs more diffusely throughout the cortex (26).

In addition to glomerulosclerosis, studies have shown that biopsies from older individuals have more ischemic-appearing glomeruli (27), more foci of interstitial fibrosis and tubule atrophy (IFTA) (16, 28), as well as more arteriosclerosis and arteriolar hyalinosis (16). These anatomic changes are likely inter-related as stenosis of small to medium arteries can cause ischemic changes both in glomeruli and tubules. As individuals age, IFTA foci develop from the attached tubules of sclerosing glomeruli and over time these foci progressively result in contraction of the cortex volume such that the IFTA density increases with age (Figure 2). Indeed, IFTA density increases with age independent of the overall fraction of cortex that contains IFTA (28). Onset of CKD at any age is superimposed on this process with increased glomerulosclerosis and IFTA beyond age-expected levels (Figure 2).

Although it seems intuitive that with glomerular loss, the size of remaining functional glomeruli will increase, this is not the case with truly healthy aging in humans (16, 20). The physiological reasons why remaining glomeruli do not undergo hypertrophy in healthy aging in humans, while such hypertrophy does seem to occur in aging (often inbred) murine species (often accompanied by lesions of focal and segmental glomerulosclerosis) (4) is not well understood, but may be due to fundamental differences in the biology of aging between humans and murine species.

Functional Changes:

An analysis of measured GFR (mGFR) studies in healthy adults suggests a decline in mGFR begins after the age of 40 years (29); However, the lack of a universal method for determining mGFR, and biological differences in mGFR in healthy persons exist across different mGFR methods (30). Given methodological differences and lack of standardization, method-specific, age-based reference limits are often needed for mGFR (31–33). In practice, there is often a reliance on estimated GFR (eGFR), but age-specific reference ranges are still needed and are typically lower than those based on mGFR (34).

Cross-sectional studies of mGFR with aging are often criticized as they cannot distinguish within-person from between-person variation in mGFR with age. However, they also can have the advantage of careful ascertainment of kidney health and absence of CKD risk factors, data often lacking in longitudinal studies. Indeed, longitudinal studies with health only required at baseline show a more rapid decline in GFR of 1.26 ml/min/1.73 m^2 per year(35) compared to cross-sectional studies where the decline is typically <1.0 ml/min/ 1.73m^2 per year (36, 37). Notably, cross-sectional studies of healthy kidney donors have consistently shown a decline in, not only the *average* GFR by age, but the upper (e.g. 97.5th) and lower (e.g., 2.5th) percentiles with age (38). If the decline in mGFR with aging is not universal but due to a subset developing clinically covert kidney disease, then the population-level variability in GFR would become wider with older age from those with covert disease having a decline in their GFR. However, this finding is not evident. Rather, the population-level variability in GFR does not increase with age but rather remains relatively constant (37). Further, the 2.5th percentile in a healthy 50-year-old woman and the 97.5th percentile in a healthy 90-year-old woman are both about 78 ml/min/1.73 m^2 (37), making it highly implausible for there to be a stable GFR with healthy aging.

As previously mentioned, an age-related increase in FGGS is evident, so an assumption is that glomerulosclerosis is linked with a decline in whole kidney GFR. However, a study of healthy kidney donors did not find evidence that age-related decline in whole kidney GFR associated with the age-related increase in nephrosclerosis or glomerulosclerosis on kidney biopsy (16, 19). More recently, this was confirmed in a cohort of patients who underwent radical nephrectomy, where authors found a decline in whole kidney GFR with age even among those with minimal amounts of nephrosclerosis (39). Since the functional nephron number declines with age and the whole kidney GFR declines in parallel, then the single nephron GFR remains relatively constant at least until about age 70 years with healthy human aging (21).

It is worth noting that kidney function has been largely defined by the glomerular filtration rate (GFR). However, other dimensions of kidney function include preventing protein loss during filtration and reabsorbing filtered proteins; reabsorbing water, electrolytes, and metabolites; preventing crystal precipitation in supersaturated urine, and endocrine/hormonal functions such as erythropoietin production. With healthy aging, there is no evidence for age-dependent protein leak into the urine (19) or increased urine crystallization with stone formation. There is evidence of a reduced range of urine diluting and urine concentrating capacity with aging (40).

UNHEALTHY AGING IN HUMANS

Structure and Function:

Unhealthy functional changes with aging can be grouped into two categories. Abnormal GFR for age and other evidence of kidney dysfunction from comorbidities and diseases that are common with aging. In particular, other evidence of kidney dysfunction includes abnormal proteinuria (or albuminuria) as this does not occur with healthy aging and should always prompt an evaluation for CKD. Unhealthy changes in GFR with aging can either be high GFR (e.g., GFR >97.5th percentile for age) or CKD (e.g., GFR <2.5th percentile for age). High GFR is an imperfect surrogate for glomerular hyperfiltration and often simply reflects a higher nephron number (38). But high GFR, especially when based on body surface area uncorrected values of mGFR (in ml/min), can be evidence of glomerular hyperfiltration as it associated with glomerular enlargement, obesity, and albuminuria (38).

Notably, the physiological healthy age-related decline in GFR is not associated with mortality. In population-based studies, a chronic eGFR of 45–59 ml/min/1.73 m^2 without significant albuminuria meets KDIGO criteria for CKD (41) but this is not associated with an increased risk of mortality for age >65 years (42, 43). A chronic eGFR of 60–74 ml/min/1.73 m^2 does not meet KDIGO criteria for CKD but is associated with an increased risk of mortality for ages 18–45 years (42). These studies, in our opinion, highlight the failure of a single eGFR threshold to identify unhealthy age-related GFR decline. Rather, age-based thresholds that can be continuous (e.g. <2.5th percentile for age in healthy adults) or simplified into categories (<45 ml/min/1.73 m^2 age >65 years, <60 ml/min/1.73 m^2 for age 40 to 65 years, and <75 ml/min/1.73 m^2 for age <40 years) have been proposed (44). However, eGFR thresholds may need to be adjusted for newer equations (45, 46).

With unhealthy aging, comorbidities and overt CKD affect the microstructural changes that impact GFR. In particular, obesity and diabetes, that are more common with older age relate to micro-structural changes, as evident by hypertrophy of glomeruli and corresponding tubules. In contrast to the normal age-related "obsolescent" glomerulosclerosis, the solidification type of glomerulosclerosis is always pathologic (47–49). When FGGS of any type is more severe than expected for age among patients with nephrotic syndrome then progressive CKD is much more likely to be observed (50). Any finding of a FSGS lesion should be regarded as a sign of unhealthy aging in humans. In addition, abnormal albuminuria (excretion rate >30mg/day), as noted above, is not a feature of normal healthy aging, even when whole kidney GFR has declined to less than 60ml/min/1.73 m^2 (but above 45ml/min/1.73 m^2) in a subject over 65 years of age (51). High GFR for age may be the consequence of concomitant obesity (52, 53) and diabetes-related hyperfiltration (54) and represent examples of unhealthy aging.

THE INTER-RELATIONSHIPS of KIDNEY AGING AND CHRONIC KIDNEY DISEASE

With the current definition of CKD, any adult person having a GFR (eGFR or mGFR) of <60ml/min/1.73 m^2 for 3 months or longer can be regarded as having CKD (41). Many apparently healthy subjects over age 65 years will meet the definition of Category 3A CKD (GFR between 45 and 59ml/min/1.73 m^2 and a uACR of <30mg/g) (44, 55). Any relationship of such a Category of CKD to excess risk of cardiovascular disease and all-cause mortality is inconsistent and very modest at best (56, 57) and likely explained by comorbidity and not GFR itself. This discrepancy has led many investigators, mainly from Europe, to suggest that these criteria for defining CKD on GFR criteria (either eGFR or mGFR) be age-adapted (43, 44). Such an age-adapted schema would lead to a substantial reduction in the estimated global burden of CKD (55). Recent studies give much support to the notion that the absence of age-adapted thresholds of GFR for defining CKD leads to overdiagnosis of this condition in older adults (42, 43, 58, 59).

To be sure, the processes involved in the generation of CKD and kidney aging share many elements in common (60). CKD may accelerate the processes involved in healthy aging and vice-versa, however, disentangling the cause-and-effect aspects can be very difficult (61).

The assessment of GFR in aging humans can be challenging. Creatinine formation and excretion decreases with age, likely a consequence of sarcopenia (62). These changes are, in part adjusted for by the age exponent in the eGFR-creatinine equations. But a simple exponential adjustment may be insufficient to account for extremes in muscle mass loss observed in frail, chronically ill elderly subjects. This can lead to an over-estimation of true GFR by eGFR-creatinine equations. The use of a Cystatin C based eGFR or a creatinine + Cystatin C based equation may improve the prediction accuracy (as assessed by the P30 metric), as Cystatin C generation/degradation seems to be much less affected by age than creatinine generation (63) at any given level of mGFR. Nevertheless, Cystatin C serum levels can also be affected by non-GFR related determinants, such as diabetes, obesity and chronic inflammation that can commonly be found in elderly subjects (64).

Endothelial dysfunction, found in unhealthy aging, may also lead to a discrepancy between the values of eGFR-creatinine and eGFR-Cystatin C due to reduced permeability of Cystatin C (Molecular weight= 13,000 Daltons) compared to Creatinine (Molecular weight=113 Daltons) at the glomerular capillary level. This hypothesis is also known as the “shrunken pore syndrome” (65), first described by Anders Grubb (66).

As mentioned above, a low nephron endowment at birth (signaled by a low birth weight of <2.5kg) or exposure to potential nephrotoxins in the peri-natal period, can lead to the occurrence of a GFR <60ml/min/1.73 m^2 earlier in life (7). The post-natal adaptation to such nephron under-endowment partially obscures the effect when whole kidney GFR measurements or estimates are used to assess kidney function. These adaptive processes lead to an increased single-nephron GFR (hyperfiltration) and glomerular hypertrophy, which can collectively cause maladaptive glomerular (podocyte) injury (often manifested by higher systemic arterial blood pressure and/or increasing albuminuria) to the remaining nephrons and thereby facilitate an accelerated loss of nephron number compared to individual with a normal nephron endowment at birth (7, 67).

SPECULATIONS ON PATHOPHYSIOLOGY: Ischemia vs Podocyte dysbiosis

It is generally accepted that visceral glomerular epithelial cells (podocytes) are post-mitotic, terminally differentiated cells, with a minimal regeneration potential. A study has shown how podocyte nuclear density was around 3-fold smaller in older kidneys compared to young kidney, although it is unclear what is the real effect of older age because not all studied individuals were healthy (68). The authors did not find evidence that ischemic glomerulopathy correlated with arteriosclerosis, but instead it correlated with higher rate of podocyte detachment. This was especially evident in glomeruli with signs of wrinkled glomerular basement membrane and glomerular collapse.

The same group showed a similar age-related decline in podocyte density in rats with hypertrophic stress(69), however, this was associated with FSGSs, a feature not found in human healthy aging. More recently, it was proposed that FSGS lesions(70), and glomerulosclerosis(71) are a consequence of a mismatch between glomerulomegaly and the capacity of podocytes to compensate and adequately expand filtration surface. The authors found that calorie restriction ameliorated glomerular growth, which in turn significantly reduced progression of FSGS lesions or slowed progression of ESKD. This finding is consistent with increased prevalence of FSGS lesions in humans with increasing obesity prevalence in the last several decades in many countries (70, 72). It seems likely that studying age-related changes in podocyte biology in both humans and murine species is hampered by concurrent obesity and comorbidities. Inbred animal raised in captivity and nurtured by a diet different from conditions in the wild might experience a form of unhealthy aging, akin to that seen in some humans.

CONCLUSIONS AND RESEARCH INITIATIVES

This review has highlighted the structural and functional changes (stressing GFR in the latter dimension) that occur in normal physiological (healthy) and co-morbidity associated

aging in humans. The detailed study of function and anatomy among healthy living donors has greatly amplified our knowledge of the kidney alterations accompanying physiological human aging, but we cannot yet pinpoint the precise mechanisms involved in these processes. Co-morbidity, such as diabetes, obesity and hypertension accompanying aging, seems to substantially alter the phenotype of the aging kidney but much deeper phenotyping and “multi-omics” will be required to better understand the mechanisms underlying these changes in the aging kidney. Chronic kidney disease and kidney aging intersect at multiple levels- including diagnosis, pathophysiology and prognosis. More detailed analysis of the tissue distribution of anatomical and pathological changes as well as molecular phenotyping may give better insight into the two-way interaction of CKD with aging. The use of a single, absolute threshold of GFR (mGFR or eGFR) to define CKD in all adults, regardless of age, needs to be re-examined.

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KEY POINTS:

- The kidney cortex and medulla volumes do not change in parallel with healthy aging, as up to 50 years of age cortex volume declines whereas medulla volume increases.
- Microstructural features of healthy aging include nephron loss, increase in globally sclerosed and ischemic-appearing glomeruli (predominantly in superficial cortex), and a higher density of small interstitial fibrosis and tubular atrophy foci.
- The single nephron GFR remains relatively constant, at least until about age 70 years.
- With unhealthy aging, comorbidities such as obesity and diabetes and overt chronic kidney disease accelerate microstructural pathology seen in aging, as well as contribute disease-specific pathology such as the solidification form of glomerulosclerosis.
- The use of a single, absolute threshold of GFR to define chronic kidney disease in all adults, regardless of age, does not account for the microstructural differences evident between healthy aging and chronic kidney disease.

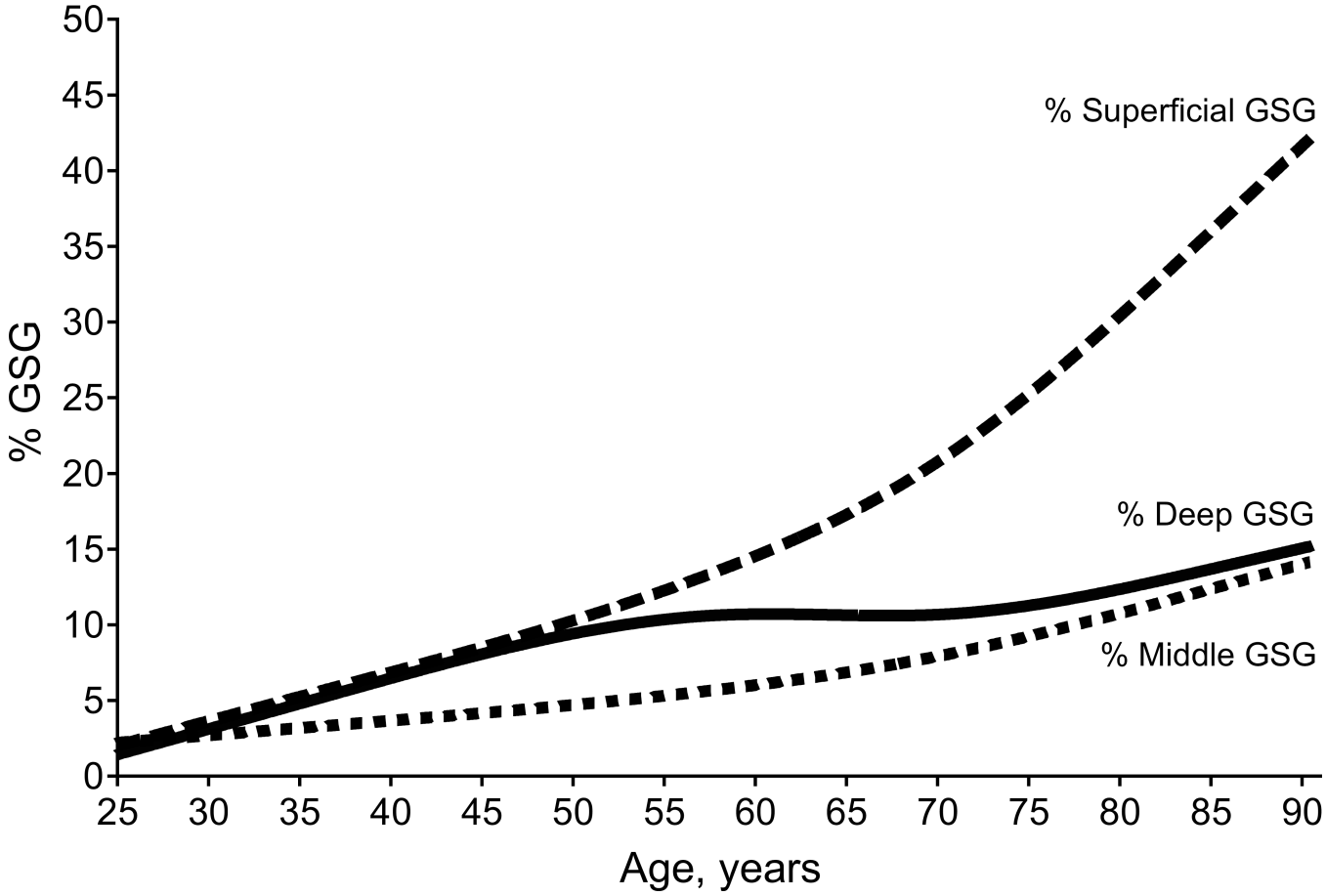

Figure 1.
Age-related global glomerulosclerosis primarily occurs in superficial cortical regions.

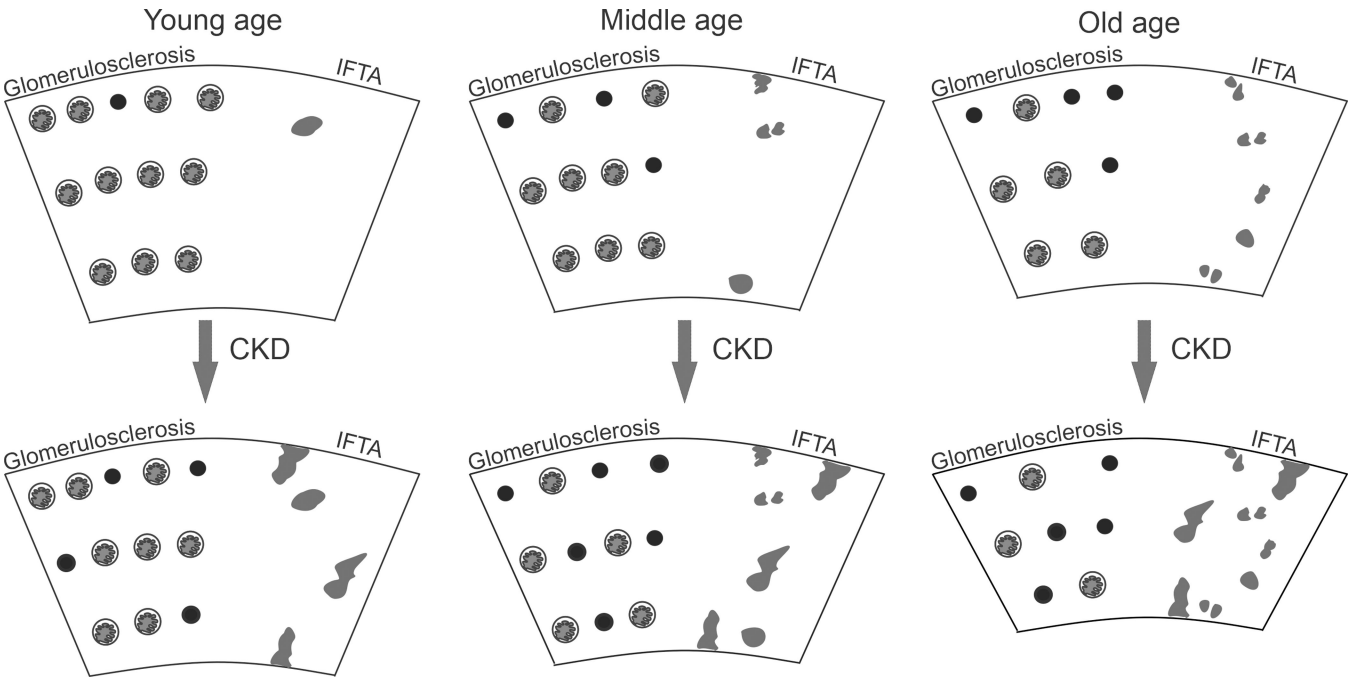

Figure 2.

With healthy aging, there is an increase in global glomerulosclerosis (predominately in the superficial cortex) and loss of glomeruli from young age to old age. There is minimal IFTA (gray areas) that atrophies over time with contraction of the cortex and an increase in IFTA density. Superimposed chronic changes from CKD can occur at any age resulting in more global glomerulosclerosis and more IFTA. Black circles denote globally sclerosed glomeruli.