Aging and Physiological Changes of the Kidneys Including Changes in Glomerular Filtration Rate

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\section*{Introduction}

Several histological and physiological changes make the aged kidney different from the young one, and they may lead to a number of clinical conditions usually observed in the old population. In the following, we describe these changes and the clinical syndrome resulting from them.

\section*{Structural and Physiological Senile Renal Changes}

Since the age of 30 years, a process of glomerular replacement by fibrous tissue – glomerulosclerosis – starts, affecting an increasing number of glomeruli with increasing age. The mesangium increases to nearly 12\% by the age of 70, and microangiographic examination shows obliteration particularly of the juxtamedullary nephrons that is followed by the formation of a direct channel between afferent and efferent arterioles (i.e. aglomerular circulation) (table 1). Arterioles show subendothelial deposition of hyaline and collagen fibers that produce intimal thickening. In the small arteries, the intima is thickened due to proliferation of the elastic tissue, the media shows atrophy and there is dysfunction of the autonomic vascular reflex.

\section*{Abstract}

In addition to the structural changes in the kidney associated with aging, physiological changes in renal function are also found in older adults, such as decreased glomerular filtration rate, vascular dysautonomia, altered tubular handling of creatinine, reduction in sodium reabsorption and potassium secretion, and diminished renal reserve. These alterations make aged individuals susceptible to the development of clinical conditions in response to usual stimuli that would otherwise be compensated for in younger individuals, including acute kidney injury, volume depletion and overload, disorders of serum sodium and potassium concentration, and toxic reactions to water-soluble drugs excreted by the kidneys. Additionally, the preservation with aging of a normal urinalysis, normal serum urea and creatinine values, erythropoietin synthesis, and normal phosphorus, calcium and magnesium tubular handling distinguishes decreased GFR due to normal aging from that due to chronic kidney disease.
Renal tubules undergo fatty degeneration and irregular thickening of their basal membrane with increasing zones of tubular atrophy and fibrosis [1, 2]. In a recent study, Rule et al. [3] have shown that the prevalence of glomerulosclerosis in healthy people (kidney donors) was 2.7, 16, 44, 58, and 73% for those very young, young, adult, old and very old, respectively. These authors found that neither kidney function nor chronic kidney disease (CKD) risk factors could explain the strong association between age and glomerulosclerosis in healthy adults.

As a result of the above anatomical changes, there is a decrease in the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF); the latter decreases disproportionately more than GFR – 10% per decade from 600 ml/min/1.73 m² in youth to 300 ml/min/1.73 m² by the age of 80. Therefore, the filtration fraction, which is the ratio of GFR/ERPF, usually increases in the elderly since the denominator (ERPF) is disproportionately lower than the numerator (GFR) [1, 2, 4].

Measurement of the GFR with 51 Cr-EDTA confirms that healthy elderly individuals have a lower GFR than young subjects. At the third decade of life, GFR peaks at approximately 140 ml/min/1.73 m², and from then on, progressively declines to an approximate rate of 8 ml/min/1.73 m² per decade. This fall in creatinine clearance (Ccr) is accompanied by a decrease in creatinine production (serum sarcopenia), and consequently serum creatinine does not increase with the progressive decrease in GFR [5]. It may be better if GFR is expressed after correcting its value for body surface area, especially in the elderly in whom body surface area is usually reduced compared with the young [4]. After Kimmel et al. [34] demonstrated that old people who were on a high-protein diet maintained normal GFR, it has been hypothesized that ‘normal’ GFR observed in some elderly could be the consequence of increased protein intake that is followed by glomerular hyperfiltration [5, 6]. It has been reported that in approximately one third of old people the GFR does not decrease with age [6], but this observation has not been confirmed by subsequent publications.

Twenty-four-hour urinary sodium output and fractional excretion of sodium are significantly greater in old people because thick ascending loop of Henle sodium reabsorption and basal plasma concentrations of renin and aldosterone, and the response to their stimuli are diminished in old age. As GFR declines with age and the amount of filtered sodium is lower than in young subjects, a salt load given to an aged person takes longer to eliminate. Additionally, since there is medullary hypotonicity in old subjects, they exhibit an inability to maximally concentrate the urine. Moreover, urinary dilution capability is also decreased in aged people. Regarding the senile renal tubular handling of potassium and urea, potassium secretion and urea reabsorption are both reduced in this aged group (table 3) [7, 8].

**Table 1. Senile hypofiltration: its mechanisms**

<table>
<thead>
<tr>
<th>Senile hypofiltration</th>
<th>Glomerulosclerosis</th>
<th>Mesangial expansion</th>
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**Table 2. Senile renal vascular changes: its mechanisms**

<table>
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<tr>
<th>Renal vascular changes</th>
<th>Renal atherosclerosis</th>
<th>Vascular dysautonomy</th>
<th>Arteriole subendotelial hyalinosis</th>
<th>Aglomerular circulation</th>
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</table>

**Table 3. Senile tubule-interstitial changes: its mechanisms**

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<tr>
<th>Tubule-interstitial changes</th>
<th>Tubular diverticuli</th>
<th>Tubular atrophy</th>
<th>Tubular fat degeneration</th>
<th>Reduced sodium reabsorption</th>
<th>Reduced potassium secretion</th>
<th>Interstitial fibrosis</th>
<th>Medulla hypotonicity</th>
</tr>
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</table>

**Senile Decrease in GFR Differs from That in Chronic Renal Disease**

It is important to emphasize that even though the aged kidney has a decreased GFR, it differs in many ways from that in patients with chronic renal failure. Thus, healthy very old persons (older than 85) and patients with CKD (stage 3) share two main physiological characteristics: a similarly low GFR (about 50 ml/min/1.73 m²), and a diminished ability for salt and water reabsorption from the renal tubule. However, despite these similarities, the aged kidney and the chronically damaged one differ markedly in a number of physiological aspects described below [9]:

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• Proximal tubular function is preserved in the healthy oldest old and their serum erythropoietin and hemo-
globin levels are normal. Conversely, anemia secondary
to a low serum erythropoietin secretion is one of
the main characteristics in CKD patients [9–11].
• Even though the fractional excretion (FE) of urea is
increased in both settings, serum urea level is normal
in the elderly while it is increased in chronic nephrop-
yth [9, 12, 13].
• Serum levels and FE of calcium, magnesium and phos-
phorus are normal in the healthy very old population,
while CKD patients usually have increased FE of these
substances, in the presence of normal magnesium, low
calcium and high phosphorus serum levels. Parathy-
roid hormone and active vitamin D levels are normal
in the healthy oldest old, while the former is increased
and the latter is decreased in the CKD population [9,
10, 13–15].
• FE of potassium increases as GFR decreases under the
influence of the aldosterone hormone in patients with
CKD. However, the FE of potassium is relatively di-
iminished in relationship to GFR in the healthy very
old people. This phenomenon has been attributed to a
relatively low serum aldosterone and aldosterone re-
sistance in healthy very old people [9, 10, 16, 17].
• Urinalysis is normal in the healthy old people, that is
they have neither hematuria nor proteinuria (lower
than 0.3 g per day). However, the level of albuminuria
may depend on the method of its assessment since if
one uses the albumin-to-creatinine ratio to assess pro-
teinuria, one may obtain a higher value due to the low-
er urinary creatinine excretion in the elderly [9].

Creatinine Renal Handling in the Elderly

Classically, it has been described that renal creatinine
excretion in humans is the result of two physiological
processes: glomerular filtration and proximal tubular se-
cretion [12]. However, there are certain physiological sit-
uations, such as in the case of healthy newborns and pre-
mature babies, and dehydrated adults, in which tubular
creatinine reabsorption has been documented [18–23].
Despite the finding of a classical study by Rowe et al. [21]
that showed that tubular secretion of creatinine did not
change with normal aging, in a recent report, Musso et
al. [22] documented a net creatinine reabsorption in the
renal tubules of healthy old persons. It is possible that the
senile tubular changes make the aged tubules more sus-
ceptible to creatinine reabsorption as it happens in new-
borns, but in this case due to tubular immaturity [1, 2,
24]. This creatinine reabsorption pattern turns into a se-
cretion one in the setting of severe chronic renal disease
[25].

Renal Reserve in the Elderly

Renal reserve is the capacity of the kidney to increase
its basal GFR by at least 20% after an adequate stimulus,
such as a protein load. An increase in plasma amino acid
levels would result in an increase in the filtered load of
amino acids at any given GFR and would provoke an in-
crease in tubular amino acid reabsorption. Because ami-
no acids and sodium are cotransported in the proximal
tubule, proximal sodium chloride reabsorption would
also increase, resulting in a decrease in sodium delivery
to the distal tubule and macula densa, which induces the
release of vasodilator autacoids, which lead to afferent ar-
teriole vasodilatation and a consequent increase in renal
blood flow and GFR [26, 27]. Musso et al. [28] docu-
mented that renal reserve is preserved in healthy very old
people, but its magnitude decreased significantly with aging.

Glomerular Filtration Estimation in the Elderly

In clinical practice, Ccr is estimated in the elderly
using either the Cockcroft-Gault equation (CG) or the
MDRD (modification of diet in renal disease) formula
[29]. When applied to the elderly, each of these formulas
has its advantages and disadvantages. CG underestimates
Ccr in very old people, while MDRD has the advantage
of not requiring the patient’s weight for calculating GFR.
Furthermore, Musso et al. [22] showed a poor correlation
between GFR obtained by MDRD and the one measured
by Ccr with cimetidine, which is a proxy of the GFR; con-
versely this study showed a good correlation between the
Ccr obtained by CG and GFR measured by Ccr with ci-
metidine. MDRD estimated GFR (eGFR) and CG esti-
minated Ccr overestimate true GFR in old people because
of the senile lean mass reduction secondary to sarcopenia
[29]. Keller [35] believes that the easiest formula for esti-
mating GFR in people between 25 and 100 years old is the
following one: GFR = 130 – age (in years) ml/min, but this
has not been verified by direct comparison with creati-
nine clearance with cimetidine [22, 30]. eGFR estimated
by cystatin C is much less than eGFR estimated by the
MDRD in the elderly and, therefore, using cystatin C
eGFR increases the prevalence of CKD in community-
based studies. Moreover, it has been demonstrated that in old persons with GFR lower than 60 ml/min, cystatin eGFR is not superior to the calculations by the CG and MDRD formulas. Alvarez-Gregori et al. [31] have recently developed an easily available and inexpensive method (HUGE formula) for differentiating CKD from the decrease in GFR associated with the renal aging process and that resulting from a disease process. This formula includes hematocrit, blood urea and gender (HUGE), and diagnoses CKD regardless of the variables of age, blood creatinine, creatinine clearance, or eGFR. The HUGE formula is: \( L = 2.51 - (0.26 \times \text{hematocrit}) + (0.12 \times \text{urea (mg/dl)}) \) (+1.38 if male). If \( L \) is a negative number, the individual does not have CKD; if \( L \) is a positive number, CKD is present. The authors have demonstrated that the HUGE formula is more reliable than MDRD and CKD-EPI, particularly in persons aged over 70. However, this method has not been validated by other investigators yet.

Clinical Consequences of Low GFR and Creatinine Reabsorption in the Elderly

- A serum creatinine concentration of 1 mg/dl reflects a GFR of 120 ml/min in a 20-year-old person and 60 ml/min in an 80-year-old [6].
- Senile hypofiltration predisposes healthy old people to cardiac failure and to lung congestion if they receive a saline load [6].
- The dose of prescribed drugs must be adjusted to the senile GFR preferably calculated by the CG formula [32].
- In old people, low GFR differs from CKD because the GFR is the expected one for the age, as well as the fact that the GFR is stable over a period of 6–12 months. In addition, on urinalysis, low GFR shows neither glomerular hematuria nor significant proteinuria (>0.30 g/day) [6].
- Contrary to what happens in healthy young persons, a measured Ccr underestimates GFR in the healthy old individual [22].
- In acute renal failure secondary to dehydration in young people, blood urea level is increased with normal serum creatinine, a situation that normalizes with rehydration. The high serum urea level can be explained by the extensive urea tubular reabsorption induced by volume contraction. However, acute renal failure secondary to dehydration in old people usually shows an elevation not only of serum urea level but also of serum creatinine, and both altered values also normalize with rehydration. The latter observation can be explained by the documented difference in tubular creatinine handling (i.e. creatinine reabsorption) in old people compared to young patients [22, 33].

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Disclosure Statement

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