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Ren sanus in corpore sano: the myth of the inexorable decline of renal function with senescence

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Changing structure of the aging kidney

The first notion of an inexorable loss of renal mass with age goes back to uncontrolled observations suggesting that the average kidney weight decreases by up to 40% from young adulthood to senescence [1]. It must be emphasized, however, that in none of these early studies were individuals with comorbid conditions excluded. These findings therefore conflict with observations where no significant decrease in renal mass was found in elderly patients who had suffered traumatic death and in whom renal disease and/or important comorbid conditions were excluded [2]. Moreover, imaging studies investigating changes of renal size and structure showed only a modest decrease until the age of 75 years, whereas thereafter kidney size, calculated volume and parenchymal thickness were clearly lower [3]. Thus, loss of renal mass with aging is moderate, at least until the age of 70 years, and it seems to affect the renal cortex preferentially.

An important factor that correlates with age-associated changes of renal haemodynamics is thought to be glomerulosclerosis—as much as 30% of glomer-

uli were found to be hyalinized or sclerosed in apparently healthy elderly individuals [4]. The results of studies on glomerular number in the human kidney have shown a high degree of variability, however, and hence only minor glomerular obsolescence was found in the elderly who had suffered traumatic death [5, 6]. Kasiske [6] also demonstrated that the severity of systemic atherosclerosis has a major impact on the degree of age-related glomerulosclerosis. Based on these findings, it has been concluded that the presence of glomerulosclerosis is indicative of subclinical renal injury from comorbid conditions affecting renal structure.

Increase of renovascular resistance as a hallmark of renal vascular aging

Although several past studies documented a decrease in glomerular filtration rate (GFR) in men as well as in women, most of these studies did not differentiate clearly between the effect of comorbid conditions and the effect of aging *per se* on renal function [7]. For example, in the seminal study by Davis and Shock [8] virtually all of the examined individuals >70 years of age had generalized atherosclerosis and/or disabling diseases, such as cancer. More recent cross-sectional and prospective studies documented only a modest decrease or even no change of GFR in the healthy elderly [9,10]. In these and other studies, many important factors accelerating the age-related decline of renal function were identified, e.g. hypertension, atherosclerosis (particularly of the lower limbs),

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smoking and even dietary protein intake (Table 1) [9,10–15]. Effective renal plasma flow (ERPF) decreases proportionally more than GFR, i.e. by ~10% per decade from young adulthood to the age of 80 years [7,10]. The decrease of ERPF does not concern all renal regions to a similar extent, however. Hollenberg *et al.* [16] found a significant decrease in the rapid (cortical) component of blood flow while medullary flow was preserved. This finding may, in part, explain the observed increase in the filtration fraction, i.e. the ratio between GFR and ERPF in elderly individuals [7,10,16], since the relative contribution of the juxtamedullary glomeruli with higher filtration fraction increases with age. The decrease in ERPF out of proportion to the change in mean arterial blood pressure with age implies that post-glomerular renovascular resistance (RVR) must be high (Table 2) [10]. Indeed, RVR was found to be significantly increased in normotensive elderly individuals without cardiovascular disease and this increase in RVR is even more pronounced in the elderly with cardiovascular comorbidity, such as hypertension and/or heart failure [10,17].

It has been proposed that the marked decrease in ERPF and increase in RVR with age results from structural changes of the renal vasculature, i.e. narrowing or even obsolescence of post-glomerular vessels [18]. In addition, renal vasodilation after administration of L-arginine, acetylcholine and dopamine is impaired markedly in the elderly [19–21]. Thus,

besides structural alterations, changes of vascular function play a pivotal role in the age-related increase of RVR. Vasodilation after administration of acetylcholine or L-arginine is known to be nitric oxide (NO)-dependent, and impaired endothelium-dependent renal vascular relaxation due to reduced NO generation was found in the elderly, particularly in the hypertensive elderly [20]. We have shown recently that accumulation of the endogenous NO synthase inhibitor, asymmetric dimethylarginine, with senescence may play a role in the age-related decrease of renal perfusion [22]. Taken together, the available data permit the conclusion that in the healthy elderly GFR is preserved to some extent, but at the expense of increasing filtration fraction in a vasoconstricted kidney. This condition is accompanied by partial non-responsiveness to vasodilatory agonists, particularly of the post-glomerular microcirculation.

Renal aging and sodium handling

During dietary sodium restriction, the elderly ultimately attain the same minimum urinary sodium excretion, but the rate of decrease of urinary sodium concentration is sluggish and, as a consequence, the net sodium loss is greater than in the young [23]. Both less efficient sodium reabsorption in the proximal tubule and/or reduced activity of the renin-angiotensin-aldosterone system may contribute to impaired sodium conservation by the senescent kidney (Table 2) [10,24]. In the normotensive elderly, inappropriately low basal and stimulated plasma renin activity are found, i.e. after salt restriction, diuretic treatment or upright posture [24]. Although salt deprivation reveals a salt-losing tendency in the elderly, renal capacity to excrete a salt load is impaired as well. Among other factors, reduced GFR and decreased generation of and/or responsiveness to natriuretic substances, like atrial natriuretic peptide, seem to play a certain role [25]. Thus, the elderly individual is characterized by a relative inability

Table 1. Factors confounding age-related changes of renal function

(Systemic) Atherosclerosis
Hypertension/left ventricular dysfunction
Glucose intolerance/diabetes mellitus
Obesity
(Latent) Heart failure
Undetected renal disease
Smoking
Dietary protein intake
Disabling diseases (?)

Table 2. Blood pressure, renal haemodynamics and plasma renin activity in young ($n=24$) and elderly normotensive ($n=29$) subjects, elderly hypertensive patients ($n=25$) and elderly patients with compensated mild to moderate heart failure ($n=14$)

	YNT	ENT	EHY	EHF
Age (years)	26 ± 3	68 ± 7 ^a	70 ± 6 ^a	69 ± 6 ^a
24hMAP (mmHg)	87 ± 5 ^a	91 ± 7 ^a	106 ± 10	92 ± 13 ^a
Serum creatinine (mg/dl)	0.9 ± 0.1 ^a	0.9 ± 0.1 ^a	1.0 ± 0.2 ^{a,b}	1.1 ± 0.2 ^b
GFR (ml/min/1.73 m ²)	121 ± 11	103 ± 11 ^a	103 ± 13 ^a	92 ± 14 ^b
ERPF (ml/min/1.73 m ²)	650 ± 85	486 ± 102 ^a	427 ± 55 ^b	377 ± 103 ^b
FF (GFR/ERPF)	0.19 ± 0.02	0.22 ± 0.04 ^a	0.24 ± 0.03 ^b	0.26 ± 0.06 ^b
RVR (mmHg/ml/min)	71 ± 9	125 ± 31 ^a	164 ± 33 ^b	162 ± 50 ^b
PRA (ng AI/ml/h)	0.75 ± 0.36	0.46 ± 0.46 ^a	0.35 ± 0.27 ^a	0.39 ± 0.20 ^a

The statistical differences are given at a P -value of 0.05; shared superscripts are not significantly different (adapted from [10]).

YNT, young normotensive; ENT, elderly normotensive; EHY, elderly hypertensive; EHF, elderly patients with compensated mild to moderate heart failure; 24hMAP, 24h mean arterial blood pressure by Spacelab; GFR, glomerular filtration rate by inulin clearance; ERPF, effective renal plasma flow by paraaminohippurate clearance; FF, filtration fraction; RVR, renovascular resistance; PRA, plasma renin activity.

to preserve sodium on the one hand and to excrete an overload of salt on the other. As a result, the range of homeostatic adaptation is decreased. This is of considerable practical importance, since elderly individuals are often threatened by salt and fluid depletion secondary to diarrhoea, treatment with diuretics, etc. On the other hand, the propensity to salt (and fluid) retention may predispose to blood pressure elevation and possibly explain the good response of blood pressure of the elderly to salt restriction and/or diuretic treatment.

The problem of monitoring renal function in the elderly

In the elderly, serum creatinine is notoriously unreliable as a precise indicator of GFR due to the fact that the daily production of creatinine is diminished as a result of reduced muscle mass. Consequently, the serum creatinine concentration will underestimate the decline in GFR with age (Table 2) [10,26]. In other words, the normal range of serum creatinine used for the general population is inappropriately high for senescent people. As a consequence, serum creatinine in the upper normal range may already indicate renal disease and impaired renal function in the elderly. A better index of GFR in the elderly may be the serum cystatin C concentration [27,28].

Estimation of the creatinine clearance according to different equations (e.g. Cockcroft–Gault formula) was shown to be unreliable in most studies, especially when very old individuals or individuals with comorbidity were examined [10,29]. This limited accuracy may be relevant when doses of drugs with renal elimination must be calculated. Although in healthy elderly subjects pharmacokinetics of drugs which are excreted via the kidneys is only slightly changed [30], in the sick elderly patient age-related changes in renal function may grossly alter pharmacokinetics of these drugs and their active metabolites. Dose reduction may, therefore, be necessary in order to prevent side effects. Because of the limitations of serum creatinine concentration as a marker of renal function, particularly in the undernourished elderly with reduced muscle mass and spuriously low serum creatinine concentration, a timed endogenous creatinine clearance should be assessed for calculations of drug dosage. However, one must keep in mind that many disabled elderly people are not able to collect a reliable timed urine sample. Regular measurements of plasma drug levels are therefore advised whenever indicated and possible.

Conclusions

More detailed knowledge on renal function at advanced age may be of importance on several accounts. Age-related changes may aggravate deterioration of renal function in elderly individuals who

happen to have renal diseases. In addition, impaired homeostasis with respect to salt (and fluid) balance has important consequences for the management of the elderly person who is exposed to the twin risks of dehydration and fluid overload. Finally, the kidney is the main route of excretion for many drugs and their active metabolites. Reduction of renal function with age underlies, at least in part, the known predisposition of the elderly to side effects of their medication, such as non-steroidal anti-inflammatory drugs [31].

Conflict of interest statement. None declared.

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Ageing as a determinant of renal and vascular disease: role of endothelial factors

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Keywords: endothelium; growth; hypertension; hypertrophy; inflammation; reversibility

Introduction

In developed countries, ageing is the most important risk factor for age and death after age 28. Age also determines the onset and development of the most prominent vascular and renal diseases, atherosclerosis and glomerulosclerosis. Increased vascular and renal

oxidative stress, and, as a consequence, abnormal activity of endothelium-derived molecules, such as nitric oxide (NO), angiotensin II and endothelin, are now recognized as important mechanisms controlling these disease processes. In this article, I will discuss current evidence for the involvement of endothelial factors in the genesis of vascular dysfunction and cardiorenal disease seen with ageing and present therapeutic approaches to actively interfere with these disease processes.

‘Ageing changes can be attributed to development, genetic defects, the environment, disease, and the inborn aging process

The latter is the major risk factor for disease and death after age 28 in the developed countries’.

Denham Harman [1].

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