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Review

The aging kidney revisited: A systematic review

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ABSTRACT

As for the whole human body, the kidney undergoes age-related changes which translate in an inexorable and progressive decline in renal function. Renal aging is a multifactorial process where gender, race and genetic background and several key-mediators such as chronic inflammation, oxidative stress, the renin–angiotensin–aldosterone (RAAS) system, impairment in kidney repair capacities and background cardiovascular disease play a significant role. Features of the aging kidney include macroscopic and microscopic changes and important functional adaptations, none of which is pathognomonic of aging. The assessment of renal function in the framework of aging is problematic and the question whether renal aging should be considered as a physiological or pathological process remains a much debated issue. Although promising dietary and pharmacological approaches have been tested to retard aging processes or renal function decline in the elderly, proper lifestyle modifications, as those applicable to the general population, currently represent the most plausible approach to maintain kidney health.

Contents

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1. Introduction

Human lifespan has substantially increased over the last century and the projected increase of elderly people over the next two future decades is impressive. Persons aged 65 years or more were 420 million in 2000 (United, 2010). By 2030, the number of these individuals is expected to be 550–973 million (US Census Bureau, 2005). By that date, elderly people will account for approximately 20%, 24.8% and 33% of the global population in the US, China and Europe respectively, exceeding the number of children below 15 years (Centers for Disease Control and Prevention, 2006). The average age is now 76.5 years in economically developed- and 65.4 years in economically developing-countries.

Population based studies documented that impaired renal function is common in the elderly. In the US population, renal dysfunction has a 15% prevalence in persons older than 70 years (Coresh et al., 2007). In the third National Health and Nutrition Examination Survey (NHANES III), 35% of the elderly population had stage 3 chronic kidney disease (CKD) (Coresh et al., 2003). The prevalence of the most severe CKD stage (stage 5 or end-stage kidney disease; ESKD) is age-dependent (Coresh et al., 2003; Kiberd and Clase, 2002). In the United States Renal Data System (USRDS) the prevalence of the age-stratum 65–74 years is 11% and 14% for those older than 75 years (National Institute of Health, 2009) and similar findings have been reported also in European cohorts (John et al., 2004; Jungers et al., 1996; Magnason et al., 2002). In this systematic review we describe the main anatomical and functional changes in the kidney associated with senescence and will provide updated information on the main molecular and biological pathways involved in renal aging. The criteria adopted for literature search and selection for this review are detailed in Fig. 1.

2. Epidemiology of renal function decline with age

Changes in renal function associated with aging have been estimated in 9 cross-sectional and in 3 cohort studies. In these studies, the annual average GFR reduction ranged from 0.4 to 2.6 mL/min (Table 1). The cross-sectional nature of most of these analyses and the fact that four of them were performed in living kidney donors (Fehrman-Ekholm and Skeppholm, 2004; Poggio et al., 2009; Rule et al., 2004, 2010), a highly selected population where the absence of CKD and other co-morbidities is a pre-requisite for kidney donation, limits the generalizability of these findings and leaves open the question whether the decline in renal function is an inexorable process.

REVIEW CRITERIA

Relevant articles were identified by searches of MEDLINE, PubMed and references from relevant articles combining the search terms "kidney" or "renal" with "aging" or "ageing" or "age" or "elderly" or "senescence". Search results were further combined with the terms "function" or "glomerular filtration rate" or "GFR" and "decline" or "impairment" or "decrease". Articles were included without language, methodology or date restriction. Only studies specifically dealing with the epidemiology, the anatomical, pathological and functional changes related with renal aging were considered.

Fig. 1. Review criteria.

In studies based on inulin clearance performed in the fifties in a group of 70 men, including healthy volunteers but also hospitalized patients affected by hypertension, cancer, arteriosclerosis and various infective diseases, the GFR was by the 46% lower in the very old (90 years) as compared to the young people (Smith, 1951) and these findings were confirmed in a survey based on urea clearance (Davies and Shock, 1950). In the Baltimore Longitudinal Study of Aging (BLSA) (Lindeman et al., 1985), a longitudinal study based on serial creatinine clearance measurements in 254 men without kidney disease or hypertension, the average decline in GFR was 0.75 mL/min/year, an estimate very close to that described in a recent cross-sectional study in 1203 living kidney donors (0.63 mL/min/year) (Rule et al., 2010). In the Baltimore study, the rate of GFR loss was tripled (~1.51 mL/min) in subjects aged 40–80 years as compared to subjects aged 20–39 years (0.26 mL/min). Similar observations were reported more recently in a longitudinal study in healthy Chinese people (Jiang et al., 2012). Both in the Baltimore (Lindeman et al., 1985) and in the Chinese (Jiang et al., 2012) study the GFR remained constant overtime in 36% and 44% of subjects respectively. In the Bronx longitudinal age study (Feinfeld et al., 1995, 1998) in very elderly subjects, just a small increase in serum creatinine occurred after 3 years in long term survivors and similar observations were reported in a subgroup of 31 subjects with mildly raised serum urea at baseline, suggesting that renal function decline may not be an obligatory consequence of the aging process. In a cross-sectional analysis of the BLSA study (Rowe et al., 1976a) focusing on 548 healthy subjects, creatinine clearance was 140 mL/min/1.73 m^2 at age 30 to fall to 97 mL/min/1.73 m^2 at age 80. In the inception cohort of the Nijmegen Biomedical Study (Wetzels et al., 2007), including 869 apparently healthy persons aged > 65 years, the annual GFR decline (as estimated by the $MDRD_{185}$ formula) was approximately 0.4 mL/min/year. In a mixed population of adults aged ≥ 65 years including participants with major co-morbidities (CKD included), the InCHIANTI study, creatinine clearance estimated by the Cockcroft formula showed a 2.6 mL/min/year decline over a 3-year follow up (Lauretani et al., 2008). Overall, these studies clearly document that on average renal function declines overtime but also show that in about one third of elderly individuals the GFR remains remarkably constant.

3. Issues with assessment of renal function in the elderly

Because sarcopenia and body weight loss reduce the daily generation of creatinine and creatinine levels are influenced by protein intake and hydration, these factors concur in making serum creatinine a suboptimal indicator of renal function in the elderly (Fliser, 2008). The reference range for creatinine considered as normal in the healthy young is inappropriately high in the elderly and serum values in the upper normal range may underlie early renal dysfunction (Kimmel et al., 1996). In 20 years old individuals a creatinine value of 1 mg/dL may correspond to an estimated GFR of 120 mL/min while the same value in 80 years-old persons might reflect an eGFR of 60 mL/min (Musso, 2002; Musso et al., 2009; Swedko et al., 2003). Traditional formulas for GFR estimation based on serum creatinine are notoriously unreliable in the elderly, particularly in the presence of multiple co-morbidities (Drusano et al., 1988; Fliser et al., 1997). In old subjects, GFR is systematically underestimated by the Cockcroft–Gault (CG) formula