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Translational Article

Special Issue on the Aging Kidney

Translational

Loss of Renal Function in the Elderly Italians: A Physiologic or Pathologic Process?

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Background. Nowadays it seems that chronic kidney disease (CKD) is outbreaking, mostly in the elderly participants. The aim of this study was to assess the progression of CKD in different ages.

Methods. We conducted a monocentric, retrospective, observational study enrolling 116 patients afferent to our outpatient clinic. Inclusion criteria: age >18 years, follow-up ≥5 years, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, and/or diagnosed renal disease and/or presence of renal damage. Patients were divided into four groups according to their age: 25–55 years (n = 27), 56–65 (25), 66–75 (42), and 76–87 (22). eGFR was calculated using the modification of diet in renal disease and the CKD-epidemiology collaboration formulas.

Results. Younger patients had a significantly longer follow-up and less comorbidities, evaluated by the cumulative illness rating scale score, compared with the other groups. There was no difference between creatinine at baseline and at the end-of-follow-up period among the groups. Even though renal function significantly decreased in all groups, we noticed a slower progression as the age increased, and the difference between basal and end-of-follow-up eGFR was minimal in the group of patients aged 76–87 years. Analyzing the eGFR of every ambulatory control plotted against the year of follow-up, we showed a more rapid loss of filtrate in the younger group. Instead, loss of renal function decreased as the age of patients increased.

Conclusions. This study demonstrates that, in elderly Italian participants, progression of CKD occurs more slowly than in younger patients. This implies that we may probably face an epidemic of CKD but that most of elderly patients diagnosed with CKD may not evolve to end-stage renal disease and require renal replacement therapy.

Key Words: Progression—Chronic kidney disease—Aging.

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CHRONIC kidney disease (CKD) is a relevant public health concern with prominent socioeconomic impact all over the world (1). According to the Kidney Disease Outcome Quality Initiative guidelines, CKD is defined as the presence of renal damage for more than 3 months, with or without a reduction in the glomerular filtration rate (GFR), indicated by abnormalities in the urinalysis or blood tests, or the reduction of GFR below 60 mL/min/1.73 m^2, independent of the underlying disease. The main indicators of renal damage are proteinuria, greater than 150 mg/24 h, and micro- or macrohematuria, the presence of leucocytes in the urinary sediment or clues of renal pathology at imaging techniques such as ultrasound, computed tomography, or magnetic resonance. At present, the classification of CKD in five stages is based on the GFR (1).

The relevance of CKD on a planetary scale is evident considering the global prevalence of the different stages: for the U.S. population, these are comprised between 5% and 45% in four groups stratified by age but they are quite variable according to sex, ethnicity, geographical origin, definition criteria and, the different methods used to estimate renal function.

However, independently from the variability of the different epidemiological studies, it is a common observation that CKD tends to become more frequent with aging. Among participants older than 70 years, the prevalence of CKD is around 45% in the United States and 38% in Europe (2–5). Even if several comorbidities, such as diabetes and hypertension, could account for the higher prevalence of renal damage in the elderly participants, the correlation between the decline of renal function and aging in normal participants has been long suspected (6). The several serum creatinine-based equations used to determine renal function use age, among other parameters, to estimate the GFR (7–9). This particular attention to age derives from the observation that renal function decreases with aging, which was first noted in 1949, when Davies and Shock (10) demonstrated that the GFR tends to decrease of about 1 mL/min/year after 30 years of age. The reason for this loss of renal function is not known but hemodynamic, functional, and structural alterations may be contributors (11). The typical histologic findings in the old participant, at light microscopy, include an increased percentage of obsolete glomeruli, tubular atrophy, interstitial fibrosis, and reduction of the arteriolar lumen diameter (11–13). The consequence of all these alterations is a reduction of the functional reserve of the kidney (12). It is true that the elderly participants, usually, present comorbid conditions that may increase their risk of developing a chronic or acute renal failure but the renal changes characteristic of aging may also be observed in age-matched healthy individuals (13). Thus, a CKD classification based on GFR alone favors the diagnosis of renal disease in the elderly participants, resulting in an apparent increase in its prevalence among participants older than 60 years (14). Moreover, this classification may lead to an overestimation of the number of people affected by CKD, prompting physicians to predict a CKD epidemic in the future. Although there is no clear way to confirm or deny this theory, it is possible that evaluating the progression toward end-stage renal disease in the elderly participants would help to clarify this issue. Thus, the aim of this study was to evaluate renal function loss among different ages to determine whether there was a difference in the rate of CKD progression in the elderly participants compared with younger patients and if the latter reached end-stage renal disease more rapidly than older patients.

Methods

We carried out a single center, retrospective, observational study screening 1500 patients attending our outpatient clinic and enrolling 116 based on the criteria listed in Table 1.

We recorded the following data at every outpatient clinic visit: gender, age at the beginning and at the end of the follow-up, baseline nephropathy (if known), length of follow-up, presence of comorbidities expressed as cumulative illness rating scale (CIRS) score (15), and number of acute renal failure episodes defined as a 50% increase in baseline serum creatinine values.

Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Patients older than 18 years	Patients younger than 18 years
Follow-up ≥5 years	Less than one ambulatory control per year
eGFR <60 mL/min/1.73 m^2 and/or histological diagnosis of renal disease and/or presence of renal damage indicated by abnormal urinalysis or blood tests	Patients presenting at the first visit with acute renal failure whose renal function normalized later with medical therapy

Laboratory tests included serum creatinine, estimated GFR (eGFR) calculated with both the MDRD and the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation, urinary protein excretion, uric acid, parathyroid hormone, total cholesterol, high-density lipoprotein cholesterol, serum triglycerides, hemoglobin, and HbA1c. Among all the pharmaceutical agents consumed by the patients, the anti-hypertensive medications and the presence of ACE-inhibitors and/or sartans and the adhesion to a hypoproteic diet were recorded.

Patients were divided into four groups according to their age: from 25 to 55 years, from 56 to 65 years, from 66 to 75 years, and from 76 to 87 years (Figure 1). Differences among the groups were analyzed using the one-way analysis of variance (ANOVA) followed by the Bonferroni post-test to compare pairs of groups. Correlations were made using the two-tailed Pearson's test with a confidence interval equal to 95%. A p value less than 0.05 was considered to be statistically significant. Data are expressed as mean ± standard deviation.

Results

The higher prevalence of female participants in the oldest group of the 116 patients may reflect their longer expectancy of life (Figure 2A and B). The time of follow-up, not less than 5 years, was longer in the younger groups, reaching a minimum average of 6 ± 0.97 years in the oldest group (Figure 2C). The comorbidity index was comparable among the older groups, whereas it was significantly lower

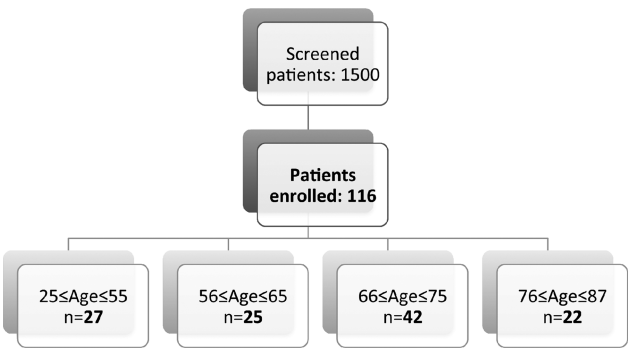

Figure 1. Study design.

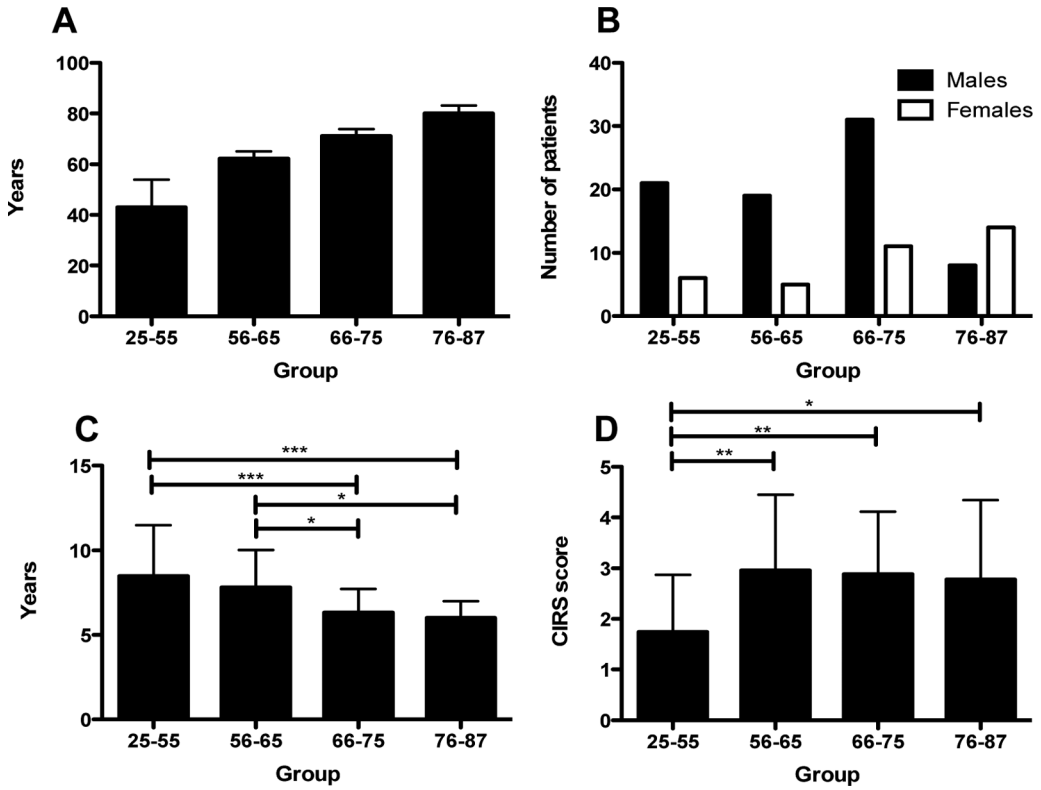

Figure 2. Panel A: average age in each group. Panel B: gender distribution in each group. Panel C: average length of follow-up for each group. Panel D: average CIRS score in each group. *$p < .05$; **$p < .01$; ***$p < .001$.

in the youngest group of patients (Figure 2D). The cause of renal disease leading to CKD was unknown in most patients with the percentage increasing with age (Figure 3D). We did not find differences among the groups with respect to baseline or end-of-follow-up period creatinine values, although all had higher creatinine values at the end-of follow-up (Figure 3A and 3B). There was a non-significant lower difference between serum creatinine at the end of the follow-up and baseline in the oldest group (Figure 3C). The eGFR was similar between the MDRD and the CKD-EPI formula, and there was a higher eGFR in the youngest group at baseline (Figure 4A and B). At the end-of-follow-up period, the eGFR was reduced in all groups compared with the baseline. However, the group of youngest patients maintained a glomerular filtrate significantly higher than the older groups (Figure 4C and D). Analyzing changes in eGFR with both the MDRD and the CKD-EPI formulas, we found that the oldest patient group conserved most of its renal function, whereas younger groups had a greater loss of filtrate along the follow-up time (Figure 5A and B). Even though all groups showed a loss of renal function, the loss was varied between the different groups, revealing that patients aged 76–87 years had a minimal progression of kidney disease, as indicated by the less steep slope of the curve (Figure 5C and D).

Discussion

The aging process is associated with structural changes in the kidney leading to a progressive reduction of its function, estimated to be approximately a 10% reduction of renal parenchyma for each decade of life during aging and a loss of function ranging from 0.4 to 1.2 mL/min of filtrate per year (16–18). Accordingly, aging of the population reflects into an increased prevalence of renal disease (19). Decreased renal function affects ~15% of participants older than 70 years (20), leading some to state that chronic kidney disease and end-stage renal disease are illnesses of aging (21,22). Data from the NHANES III study revealed that ~35% of people older than 70 years have Stage 3 CKD (3). It remains unclear whether loss of renal function was the result of physiological aging or a consequence of cardiovascular alterations and risk factors commonly associated with CKD such as hypertension, diabetes, and smoking. The results of this study demonstrate that elderly people with reduced renal function progress significantly more slowly toward end-stage renal disease than younger patients. The average serum creatinine and the GFR, independently of the equation used to estimate it, change during the 5 years of follow-up but much less in the oldest group compared with the younger groups. The reduction of eGFR is similar to the physiological loss of filtrate

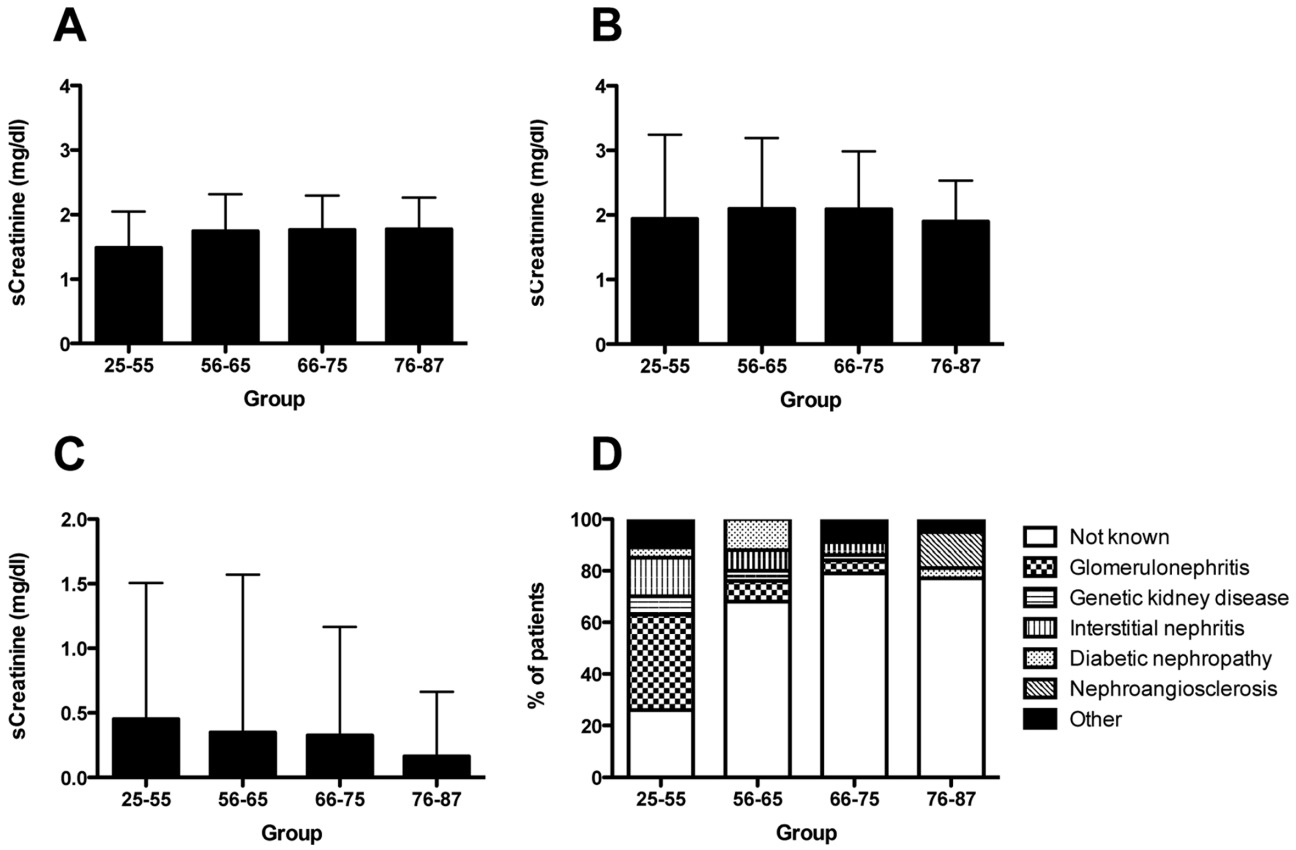

Figure 3. Panel A: average baseline serum creatinine values. Panel B: average serum creatinine values at the end-of-follow-up period. Panel C: mean difference between serum creatinine at the end of follow-up and the baseline value. Panel C: percentage of patients according to renal disease in each group.

reported in other studies on aging in the apparently healthy general population, a surprising finding because the elderly participants in this study had a reduced glomerular filtrate at baseline. Patients enrolled in the oldest group were followed in our outpatient clinic and received currently available treatment aimed at conservation of renal function, as did younger patients. This leads us to conclude that the progression of CKD in the elderly participants is slower than in younger patients, even if the elderly participants had more risk factors such as cardiovascular diseases and hypertension. We speculate that, perhaps, elderly patients included in this study do not have a chronic renal disease but have a reduction of renal function compatible with their age. The CKD classification, indeed, is based on the GFR value that is usually estimated using equations that penalize the more advanced ages of life. In addition, using eGFR to define CKD could be misleading. A reduction of renal function not associated to significant alterations in the urinalysis should not be considered kidney disease. CKD Stages 3–5 are defined exclusively on the basis of GFR. Thus, any individual with an eGFR less than 60 mL/min for more than 3 months will be considered as a CKD patient. Our study included patients with a decreased eGFR and abnormalities in the urinalysis, however a minimal proteinuria could be found in hypertensive patients as well as in normotensive patients without renal impairment. Thus, the slow disease progression rate could be simply attributed to the lack of disease. Another possibility could be the loss of muscle mass. We know that aging is characterized by a progressive reduction of muscular mass leading to a decreased production of creatinine and, in turn, to a reduced serum creatinine concentration (23–26). Consequently, serum creatinine in the elderly participants may increase less with a slower decrease of glomerular filtration. This only apparent slow progression may induce to the wrong conclusion that CKD in the elderly participants usually shows a more benign course. Unfortunately, we did not evaluate body weight and muscular or fat mass in our patients, measurements that could be done in a prospective trial. Our results are perfectly in line with other studies, such as the Baltimore Longitudinal Study on Aging that reported a decline in creatinine clearance of about 0.75 mL/min/year after the third decade of life with about one third of participants showing a stable renal function more than 20 years of follow-up (27). Another study reported a decline in renal function close to 1.05 mL/min/year in participants aged 70–110 years (28). Finally, results from the Cardiovascular Health Study indicated that there is

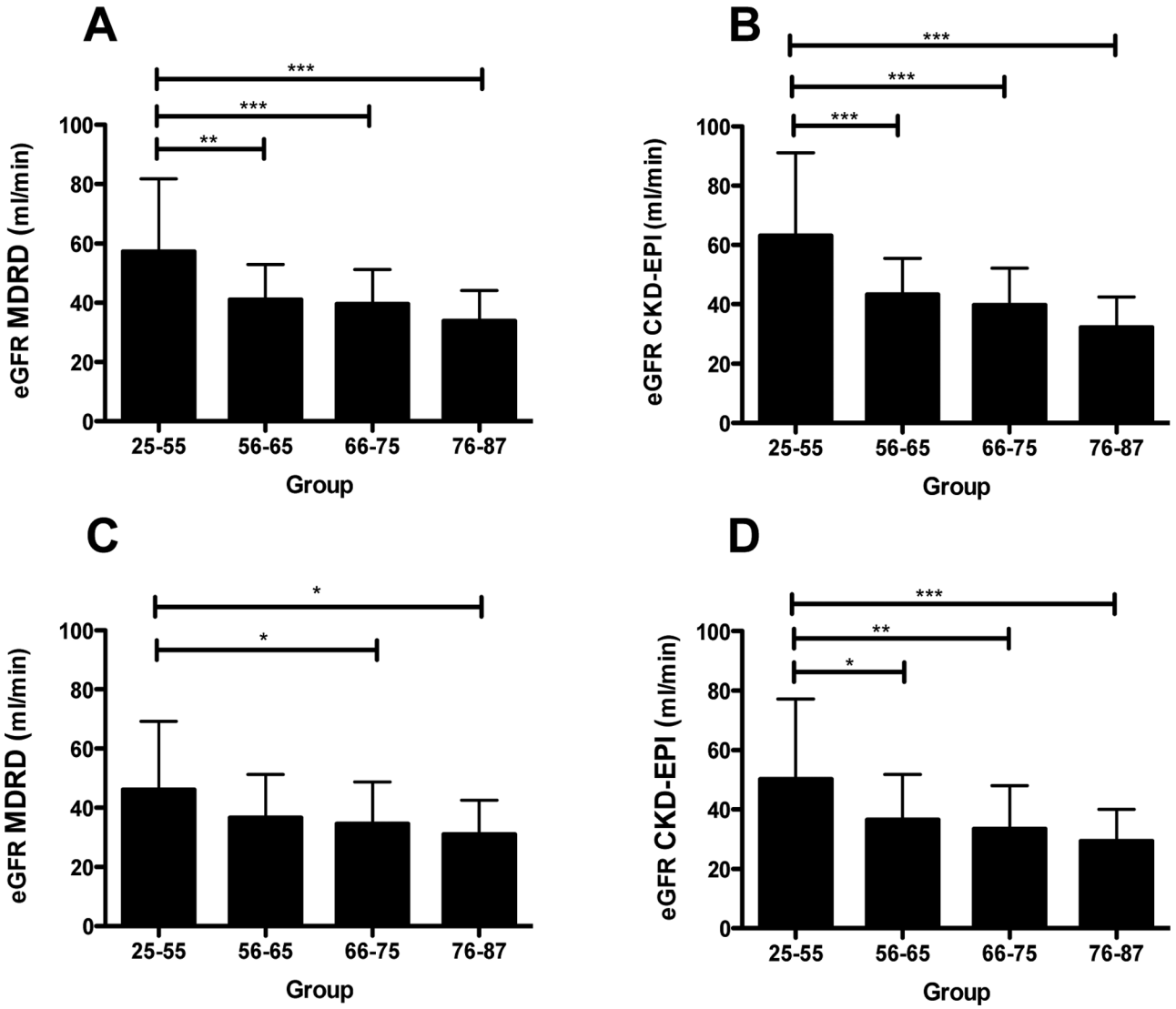

Figure 4. Panel A: average baseline eGFR according to the MDRD formula. Panel B: average baseline eGFR according to the CKD-EPI formula. Panel C: average eGFR at the end of the follow-up according to the MDRD formula. Panel D: average eGFR at the end of the follow-up according to the CKD-EPI formula. *$p < .05$; **$p < .01$; ***$p < .001$.

no progression of chronic renal disease in the majority of elderly participants enrolled with a mean age of 73 years (29). The mechanisms inducing renal fibrosis during aging and leading to glomerular sclerosis, interstitial fibrosis, vascular alterations and, finally, a reduction of renal function are incompletely understood. Nonetheless, in animal models, collagen deposition, at the glomerular or interstitial and vascular level, seems linked to an enhanced transcription of the gene coding for the Collagen III isoform (30). This transcriptional increase can be prevented, always in animal models, by caloric restriction and this prevents also glomerulosclerosis and tubulo-interstitial fibrosis. Moreover, caloric restriction prolongs life expectancy and reduces cardiovascular complications in rats (31). Finally, in rats, caloric restriction leads to a reduction of proteinuria and mesangial matrix deposition (32). Actually, this series of events could be operating also in elderly humans. It is known that caloric intake is reduced in the elderly participants (33,34). A reduced caloric and, therefore, protein intake implies a diminished intake of dietary components known for their pro-oxidant and pro-inflammatory activity such as advanced glycation end-products (AGEs). AGEs form by non-enzymatic glycosylation of long-living protein but are also introduced through the diet (35–38). It has been demonstrated that AGEs can induce matrix deposition and sclerosis altering mesangial cells (39). The slow progression of CKD in the elderly participants could be a consequence of the reduced AGE intake via the diet as these participants have a reduced caloric/protein intake. Glomerular hyperfiltration is another mechanism frequently advocated to be responsible for progression of CKD. As demonstrated by

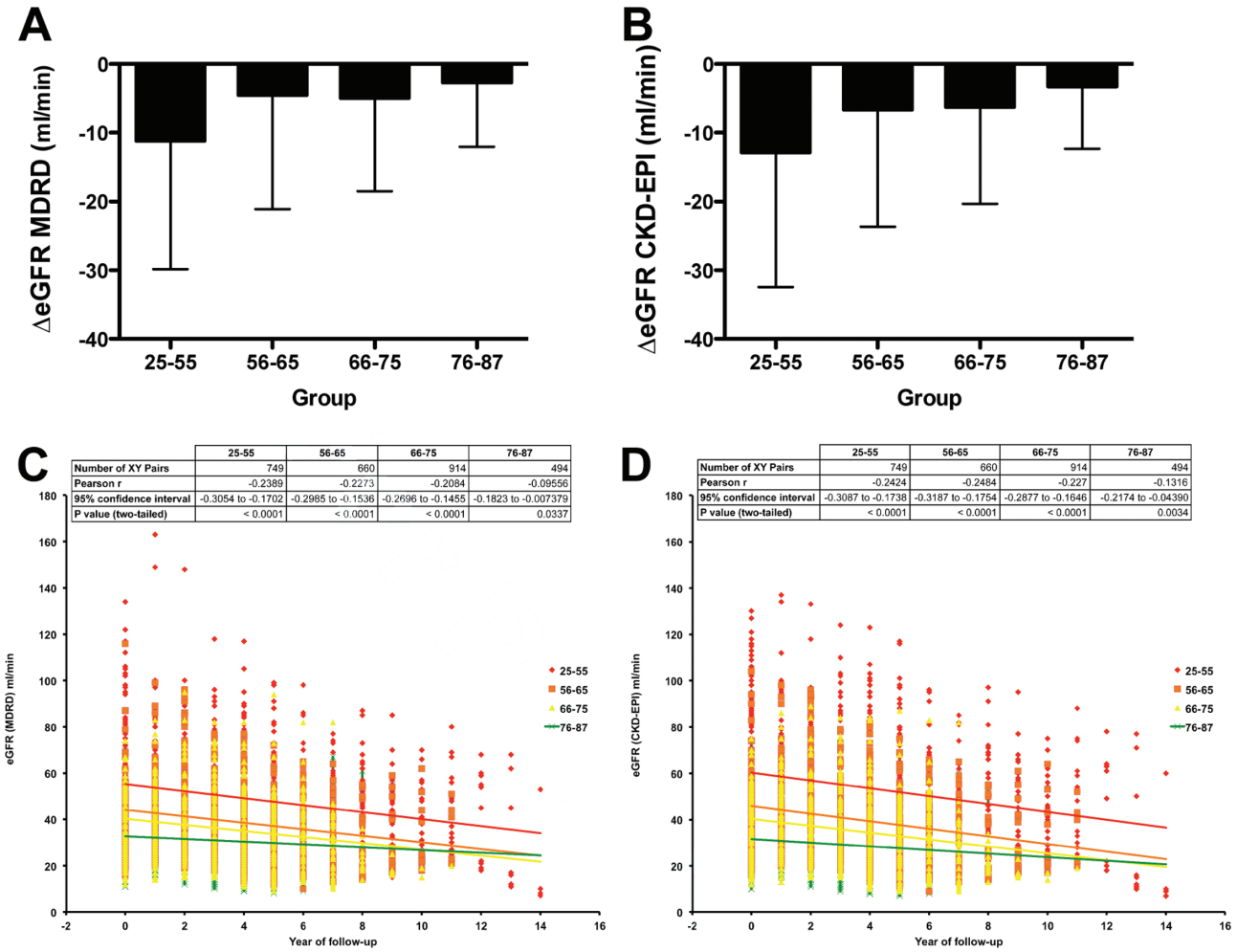

Figure 5. Panel A: average difference between baseline and end-of-follow-up eGFR according to the MDRD formula. Panel B: average difference between baseline and end-of-follow-up eGFR according to the CKD-EPI formula. Panel C: loss of renal function in different groups of age according to the MDRD equation. Panel D: loss of renal function in different groups of age according to the MDRD equation.

Brenner (40) and colleagues, a reduction in renal mass is associated with compensatory hyperfiltration in the spared nephrons. Increasing pressure inside the glomeruli progressively leads to matrix deposition and, in turn, to sclerosis. According to Brenner's (41) and other later studies, a low protein diet was able to reduce compensatory hypertrophy and hyperfiltration. Elderly people could take advantage of this phenomenon. As a matter of fact, elderly kidneys could be compared with a model of reduced renal mass; therefore, a reduced protein intake could reduce hyperfiltration and slow down the progression of renal disease. Obviously, the reduced renal function in the kidneys of elderly participants must not be underestimated because it has been associated with an increased mortality from all causes and from cardiovascular disease (42). Moreover, the risk of death among participants with similar eGFR is greater in the elderly participants (43). Finally, old patients with a reduced renal function are more likely to develop acute renal failure and reiterated insults to the kidney could lead to a rapid progression of CKD to end-stage renal disease (44).

In conclusion, our study demonstrates that, in elderly participants, progression of CKD occurs more slowly than in younger patients. This implies that we may face an epidemic of CKD and that most of elderly patients diagnosed with CKD may not evolve to end-stage renal disease and require renal replacement therapy. A note of caution is that elderly patients with a mild reduction of renal function should be closely followed by their family physician because they are at greater risk of developing acute renal failure and cardiovascular mortality.

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