

## Nephroprotection in the oldest old with chronic kidney disease: Special considerations

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### Abstract

Nephroprotection strategies are crucial for handling chronic kidney disease (CKD) complications, and slowing its progression. However, these preventative measures should be guided by major geriatrics principles in order to help nephrologists to adequately handle the oldest old with CKD. These geriatric concepts consist of taking into account the relevance of choosing an individualized therapy, handling clinical frailty, and keeping a geriatric perspective which means that a good quality of life is sometimes a more important therapeutic objective in

octogenarians than merely prolonging life. Even though nephroprotection strategies for treating the oldest old with CKD are basically similar to those applied to younger patients such as low sodium and protein diet, optimized hemoglobin levels, blood pressure and metabolic control, the treating physician or care provider must at all times be ready to make fundamental adjustments and tweak patient care paradigms and objectives if and when the initial therapeutic options applied have caused unintended clinical consequences and complications. Additionally, the sarcopenia status should also be evaluated and treated in very old CKD patients.

**Key words:** Oldest old; Very old; Nephroprotection; Chronic kidney disease; Chronic nephropathy

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**Core tip:** Even though nephroprotection in the oldest old is basically similar to those applied to younger patients, it should be performed applying a geriatric perspective, where good quality of life is sometimes a more important therapeutic objective than merely prolonging life.

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### INTRODUCTION

Nephroprotection strategies are crucial for handling chronic kidney disease (CKD) complications, and slowing its progression<sup>[1,2]</sup>. The term "CKD" is inter-

preted as a estimated glomerular filtration rate < 60 mL/min per 1.73 m<sup>2</sup> measured by the modification of diet in renal disease equation and/or presence of proteinuria, at least 1+, on dipstick urinalysis<sup>[3]</sup>. The term “nephroprotection” is defined as all those habits, diets, and medications which are currently proposed as useful therapeutic tools for achieving this purpose, such as avoidance of sedentary lifestyles, smoking, high sodium and high protein diets, as well as effectively managing disease states such as hypertension, dyslipidemia, hyperglycemia, and hyperparathyroidism<sup>[1,2]</sup>. However, these preventative measures should be guided by major evidence-based geriatrics concepts in order to help nephrologists to adequately handle oldest old people with CKD<sup>[2,4-9]</sup>. In this article, the “oldest old” is defined as people older than 79 years, according to the definition adopted by the most relevant literature in this field<sup>[10,11]</sup>. The first geriatric concept involved in this care model consists of the relevance of choosing an individualized therapy since treatment outcomes in the oldest old are influenced by many clinical variables which can persuade nephrologists to use alternate therapeutic approaches for treating patients in this category. Such variables include changes secondary to ageing (immunesenescence, reduced glomerular filtration rate and reduced hepatic metabolism), polypharmacy (use of  $\geq 6$  medications), prevailing elderly diseases (depression, visual and hearing impairment), and the concomitant presence of other geriatric syndromes (delirium, falls, and postration)<sup>[7,12-16]</sup>.

The second geriatric concept consists of prescribing treatment paradigms under a geriatric perspective. This means that a good quality of life is sometimes a more important therapeutic objective in octogenarians, than merely achieving a lower mortality<sup>[2]</sup>. This does not mean that very old patients should be undertreated but that their treatment should be adjusted to their real biological expectations, while being cognizant of the increased potential for therapeutic adverse effects<sup>[2]</sup>. Finally, the third geriatric concept refers to the imperative for taking into account the notion of clinical frailty in the elderly. Frailty is an entity which appears as a consequence of many causes and it is characterized by a reduction in strength and endurance, making people prone to lose autonomy and to die<sup>[9]</sup>. Such therapeutic strategies are based on the prescription of low intensity resistance and aerobic physical exercises, together with adequate nutrition, appropriate vitamin D supplementation, and the avoidance of polypharmacy, all of which measures may help prevent or delay the onset of this syndrome<sup>[9,15,17]</sup>.

In the present article, we have expanded on the following particular therapeutic targets to include the following-dietary salt, serum hemoglobin, blood pressure, glycemic control and lipid management-in the oldest old with CKD patients (Table 1).

**Table 1 Therapeutic targets for oldest old chronic kidney disease patients**

	<b>Targets</b>
Diet	Low-normal sodium Low-normal protein
Hemoglobin (g/dL)	11-12
Blood pressure (mmHg)	150/140-80
Hemoglobin A1C (%)	7-8.5

## DIETARY SALT

There is a trend to sodium urine loss in the elderly due to their reduced sodium reabsorption capability at the thick ascending limb of the loop of Henle and collecting tubules<sup>[18]</sup>. Consequently, it is important to take into account that when the oldest old become salt restricted (50 mmol/d), they may develop hyponatremia (senile sodium leakage hyponatremia), volume depletion (orthostatism, hypotension), and even acute renal failure<sup>[19,20]</sup>. Whereas low sodium diet is one of the cardinal features of nephroprotection<sup>[19]</sup>, this paradigm of care, when applied to the oldest old should be followed by monitoring blood pressure, serum sodium level, and renal function in order to rule out any of the above mentioned complications. If and when such unintended consequences are detected, a normal sodium diet would then be a better prescription for the specific oldest old patient with CKD<sup>[19,20]</sup>.

## SERUM HEMOGLOBIN

It has been reported in the literature that the presence of anemia can exacerbate several existing geriatric syndromes together with exaggerating neurocognitive dysfunction<sup>[21]</sup>. Therefore the oldest old often do not tolerate reduced serum hemoglobin levels as such low hemoglobin levels could negatively impact on gerontological functional test [activities of daily living (ADL) and instrumental ADK], and furthermore lead to an increased tendency to develop delirium and/or falls<sup>[22,23]</sup>. Thus, the application of a target serum hemoglobin level of 11 g/dL, or less, as part of nephroprotection strategy in the oldest old must be followed by monitoring their cognition status and gait pattern in order to exclude de novo appearance of those geriatric syndromes that are enhanced by anemia<sup>[21-24]</sup>. If this situation is documented in a particular older old with CKD, a higher serum hemoglobin target (11.5-12 g/dL) will therefore represent a reasonable alternative of care.

## BLOOD PRESSURE

Meta-analysis of observational studies indicate that the incidence of stroke, myocardial infarction, and overall mortality increased with increasing blood pressure in

old and very old patients, although the observed relative risk decreased with increasing age<sup>[25]</sup>. Additionally, the INVEST study highlighted a J-shaped relationship between systolic and diastolic blood pressure and outcomes in hypertensive old people suffering from coronary arterial disease<sup>[25]</sup>. The risk of mortality in patients aged  $\geq 80$  years increased when systolic blood pressure was  $< 140$  mmHg or diastolic blood pressure  $< 70$  mmHg<sup>[25]</sup>. Although it has been documented that anti-hypertensive treatment in the oldest old was associated with a reduction in the frequency of strokes and major cardiac events, there was however no benefit in cardiovascular death nor in general mortality<sup>[26]</sup>. Furthermore, the evidence-base provided by several studies (INVEST, STONE, HYVET) is reassuring regarding targeting relatively higher blood pressure levels in the very elderly-blood pressure target  $< 150/80$  mmHg-although these aforementioned studies did not specifically address CKD patients<sup>[25]</sup>. Nonetheless, it has been recommended that target blood pressure in the oldest old with CKD should be  $< 150/90$  mmHg in non-albuminuric patients, and  $< 140/80$  mmHg in albuminuric ones<sup>[25]</sup>. Very importantly, these blood pressure goals should be reached gradually, and the treating physician must always take into account each individual patient's comorbidities<sup>[7,17]</sup>. This is to avoid the interdependence phenomenon between diseases (comorbidities worsen each others) usually observed in the elderly and their reduced tolerance to medication; since treatment of hypertension in the oldest old can induce orthostatic hypotension, falls with bone fractures, and the exacerbation of renal failure which sometimes then is not reversible on drug discontinuation<sup>[20,27-46]</sup>. In this sense, it has been reported in the literature a clinical entity termed "normotensive acute renal failure" which consists of an acute GFR deterioration in CKD elderly when their blood pressure is reduced to normal range. This phenomenon has been attributed to reduced kidney perfusion secondary to senile renal dysautonomy<sup>[47]</sup>. Moreover, it is worth noting here that concomitant sodium sensitivity and endothelial dysfunction are increased in the very elderly population, and therefore low sodium diet (used with caution) and exogenous nitric oxide donors are often useful for treating resistant hypertension in this group<sup>[17]</sup>. Other antihypertensive drugs such as thiazides, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and aldosterone antagonists should be used with caution in this population, more so when GFR is below 30 mL/min per 1.73 m<sup>2</sup> due to the risk of further GFR reduction precipitating renal failure which may be irreversible, together with the complicating electrolytes and acid-base disorders<sup>[20,25-48]</sup>. The syndrome of rapid onset end stage renal disease (SORO-ESRD), a new syndrome of unanticipated acute yet irreversible ESRD, which we first described in 2010, is known to be more prevalent in the older CKD patient, and is associated with exposure to nephrotoxic agents

including ACEIs and ARBs<sup>[37,38,42,43]</sup>.

## HEMOGLOBIN A1C

Elderly people are at high risk for developing diabetes mellitus because of the following two mechanisms: insulin resistance and pancreatic islet senile dysfunction<sup>[49,50]</sup>. Besides, ageing alters the counter-regulatory responses to hypoglycemia in non-diabetic people; furthermore during hypoglycemic episodes, symptoms begin at higher levels of glycemia and they are more intense in young people, while psychomotor coordination is more affected in old individuals<sup>[50]</sup>. Additionally, diabetes mellitus is usually associated with high comorbidity in old people, and this subgroup cannot obtain cardiovascular benefit from strict glycemia control<sup>[49,50]</sup>. Moreover, therapeutic strategies with less stringent A1c levels are therefore needed in the oldest old diabetic patients since this subgroup of patients assist double to the hospital due to hypoglycemia episodes than the general diabetic patients, and it has also been documented that hypoglycemia is related to cognitive impairment in the elderly<sup>[49,50]</sup>. Thus, the consensus recommendation is a hemoglobin A1c target  $< 8\%$  for elderly patients (not  $< 7\%$  as is usually recommended for young adults) or for those patients with major complications and/or comorbid conditions<sup>[50]</sup>. Finally, a hemoglobin A1C target of 8%-9% has been recommended for patients with low life expectancy ( $\leq 5$  years)<sup>[50]</sup>.

## LIPID METABOLISM

Regarding lipid lowering therapy in this population, an interesting study in very elderly patients documented a 15% reduction in coronary events with pravastatin. This suggests, that this drug can be prescribed in the oldest old suffering from diabetes mellitus except in those with very poor life expectancy<sup>[50]</sup>.

## MISCELLANEOUS-PROTEIN DIET AND EXERCISE

Although energy needs decline with age, very elderly people can be exposed to malnutrition because of anorexia, impaired taste and smell, chewing and swallowing problems, geriatric syndromes and senile prevalent comorbidities which lead to difficulties for cooking and eating<sup>[24,50]</sup>. Because of the above predicated reasons, caution must be employed when overly restrictive eating patterns (including renal sparing low protein diet) are applied since such practices may further contribute to malnutrition in the oldest old with CKD. The interventions for improving nutritional status in the oldest old patients consist of using smaller but more frequent and fortified portions of food, and/or adding nutrition supplements between meals<sup>[24,50]</sup>. Additionally,

senile sarcopenia is a prevalent entity which can worsen with low protein ingestion, as well as with other ageing-associated comorbidities, such as diabetes mellitus<sup>[51]</sup>. Conversely, adequate physical activity, adjusted to the individual patient's clinical situation, can further improve functional status even in patients with poor health status<sup>[50,51]</sup>.

## OVERALL MORTALITY IN VERY ELDERLY PEOPLE

Even though, there is some limitation of ascribing a single pathology as the cause of death in very elderly people since concomitant multiple diseases are very common in this age group, many studies have documented cardiovascular (31%-54%), oncologic (20%-25%), and respiratory (10%-15%) diseases as the first, second, and third causes of death, respectively<sup>[10,24]</sup>. However, studies performed in centenarians (people older than 90 years) have documented respiratory disease (48%-52%), particularly pneumonia, as the main cause of death. Besides, it has been observed that the higher cardiovascular causes of death in the very elderly people are acute myocardial infarction, and cardiac insufficiency secondary to cumulative damage from ischemic heart disease. Regarding oncologic diseases, malignancies of the digestive tract: primarily gastric, esophageal, and colorectal cancer, are the most frequent oncologic causes of death in very old people. Additionally, the remaining major causes of death in very elderly people are: cerebrovascular disease, Alzheimer's disease and related dementias of later life<sup>[10,24]</sup>.

## CONCLUSION

Even though nephroprotection strategies for treating the oldest old with CKD are basically similar to those applied to younger patients, it is recommended that the managing physician must always individualize patient care. The treating physician or care provider must at all times be ready to readjust and tweak care paradigms and objectives if and when the initial therapeutic options applied have caused unintended clinical consequences and complications.

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