REPLACEMENT THERAPY AND ITS COMPLICATIONS IN OLDER ADULTS

S. Lai¹, P. Andreozzi², G. Innico³, M. Mangiulli¹, Y. Esposito¹, P. Protopapa¹, A. Perrotta¹, V. D’Ambrosio³, A. Currado¹, F. Aucella⁴

¹Department of Clinical Medicine; ²Department of Cardiovascular, Respiratory, Nephrological, Anesthetic and Geriatric Sciences, Sapienza University of Rome, Rome; ³Department of Medicine DIMED, University of Padua; ⁴Nephrology and Dialysis, IRCCS, “Casa Sollievo della Sofferenza”, San Giovanni Rotondo, Foggia, Italy

The Chronic Kidney Disease (CKD) is a common condition with a growing prevalence all over the world, particularly in patients above the age of 65 that represent the prevalent category among dialyzed population. Moreover, in the last few years, an increase of “old elderly”, patients above the age of 75 has been reported, representing the 20% of dialysis patients in the USA and UK records, and 17-24% in Italian records. Cardiovascular disease represents the most common cause of morbidity and mortality in CDK patients, with a risk of cardiovascular death higher by 10-100 times in dialysis patients than in the general population. This increase is not completely explained by traditional cardiovascular risk factors, but may in part be mediated by nontraditional risk factors, such as sarcopenia, malnutrition, frailty, cognitive impairment, particularly frequent in older adults, that could worsen the clinical prognosis. Therefore we should consider particular and important aspects of this population, such as sarcopenia, malnutrition, frailty, cognitive and psychological impairment, in order to improve the cardiovascular prognosis and to reach a good quality of life. Moreover, it is important to improve doctor/patient relationship in order to agree with the patient and his family, an appropriate replacement therapy, and if possible an appropriate “end of life”, in addition to achieving a greater adherence to therapy. The achievement of these objectives requires an organized work in multidisciplinary teams with geriatricians, nutritionists, specialist palliative care, psychologists, psychiatrists and neurologists, that evaluate overall the geriatric patient, with a better quality of life, a greater adherence to therapy and probably a reduction in healthcare spending.

Key words: chronic kidney disease, older adults, sarcopenia, malnutrition, Kidney transplantation

Chronic kidney disease in older adults

The Chronic Kidney Disease (CKD) is a common condition with a growing prevalence all over the world, especially among the adult population above the age of 70, where the prevalence in the USA, Europe and China is 47%, 35% and 28% respectively (1-2). In Italy the CARDHES STUDY (Cardiovascular risk in Renal patients of the Health Examination Survey) has reported a prevalence in the general population of 7.5% for men and 6.5% for women (3). Patients above the age of 65 represent the prevalent category among dialyzed patients and they tend to increase in developed countries’ records (4-5). However, in the last few years, in addition to a general increase of elderly patients, an increase of patients above the age of 75 (the so-called
“old elderly”) has been reported. The “old elderly” nowadays represent the 20% of dialysis patients in the USA and UK records. The Italian Record shows similar measures of prevalence and incidence in patients above the age of 75, such as 24% and 17% (Italian Record, www.sin-italia.org)(6-7). Cardiovascular disease represents the most common cause of morbidity and mortality in patients with CDK, with a risk of cardiovascular death higher by 10-100 times in dialysis patients than in the general population (8). For that reason, in the last few years particular and/or frequent problems, that could have worsened the clinical prognosis, have been studied in older adults.

**Sarcopenia, dynapenia, malnutrition and frailty**

Sarcopenia, dynapenia, malnutrition and frailty are common conditions in older adults, especially in CKD patients. The European Work Group of Sarcopenia in Old Patients (EWGSOP) (9-10) described sarcopenia as a loss of muscular mass and a decrease of functional quality in addition to a contractile failure and metabolic and endocrine abnormalities, affecting the whole metabolism, including the immune and inflammatory response (11). The prevalence of sarcopenia in clinical trials changes depending on the chosen definition, considering the loss of the 8% of the muscular mass every ten years until the age of 70, with a consecutive loss of the 13-24% every ten years (12-14) and the loss of the 50% of muscular mass in dialyzed patients, where it is often ignored or under diagnosed (15). A lot of CKD-connected conditions are able to accelerate muscular loss such as metabolic acidosis, low protein diet, no physical activities, insulin resistance, osteoporosis and Vitamine D deficiency (12-13). An important role was also attributed to a low grade chronic inflammation, since it is an important pathogenetic factor of accelerated atherosclerosis in CKD (16). Protein-energy wasting (PEW) is another frequent problem in older adults with CKD (18-75%), especially if they are treated with renal replacement therapy (17). PEW’s causes in CKD are various (Table 1) and they can lead to a syndrome called “Malnutrition-Inflammation Complex Syndrome” (MICS) or to “Malnutrition-Inflammation-Atherosclerosis” syndrome (MIA) with a worse quality of life and an increased morbidity and mortality (18-19). Therefore it is recommended a routine assessment of the nutritional status to diagnose and manage the MICS through various methods, such as the Subjective Global Assessment (SGA), the malnutrition inflammation score (MIS), composed of four sections (nutritional history, physical examination, BMI and laboratory tests), that correlates with nutritional status, inflammation and mortality in dialyzed patients (20), the Geriatric Nutritional Risk Index (GNRI), which considers albumin’s values and the relationship between current weight and ideal weight according to Lorentz’s formula and it is also able to predict the risk of complications and malnutrition-related mortality (20).

Another common condition in elderly patients is frailty, a biological syndrome characterized by a reduced reserve and resistance to stress factors. It is caused by a multiple physiological-systems failure and it can cause frailty to negative events. The expression «frail elderly» was used for the first time in 1974 by the Federal Council of Ageing and since then, a lot of definitions were attributed to it, but Fried et al. (21) were the first to define a frail phenotype and to separate it from co-morbidities and disability.

Frailty, malnutrition, sarcopenia and dynapenia are associated with reduced physical per-

<table>
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<tr>
<th>CAUSES OF PROTEIN-CALORIE MALNUTRITION IN CHRONIC KIDNEY DISEASE</th>
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<tbody>
<tr>
<td>Anorexia, Insulin resistance, Diabetes</td>
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<tr>
<td>Vitamin D Deficit, Hyperparathyroidism</td>
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<tr>
<td>Inflammation, Metabolics acidosis, Anemia</td>
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<tr>
<td>Excessive dietetics prescription</td>
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<tr>
<td>Volume overload</td>
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<tr>
<td>Factors associated with dialysis (Idiosyncrasy to some components of dialysis circuit, Dialysis membrane, A-V Fistula)</td>
</tr>
<tr>
<td>Comorbidities: age, diabetes mellitus, cardiovascular diseases, neurodegenerative diseases, hematological diseases, infections</td>
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Replacement therapy and its complications in older adults

Performances, disability, a worse quality of life and reduced survival. They can be caused by ageing, CKD or both conditions, indeed, some aspects of CKD, as modified protein metabolism, inflammation, oxidative stress and anemia, are more likely to accelerate the ageing process, leading to frailty (22). In these patients, the nutritional support (for example with food integrator) is essential (19), but in the last few years, physical activity has become more important. Constant and moderate physical activity should be encouraged and frequently monitored in these patients, considering any possible orthopedic, cardiovascular or neurological limitations by giving self-report questionnaires ([Short Form-36 (SF36), Patient Reported Outcomes Measurement Information System (PROMIS), Katz, Independence in Daily Living questionnaire (ADL), Lawton, InstrumentalActivities of Daily Living (IADL)], by diagnostic procedures (cardio-pulmonary test, muscular assessment) and by giving «field test» to evaluate motility and physical abilities (GaitSpeed, WalkingTests, Chair Stands etc) (23).

Dialysis or conservative-palliative therapy

Frailty, malnutrition and sarcopenia have a strong negative impact on health conditions and on prognosis of older adults patients, influencing the choice of renal replacement therapy (24-25). The choice between starting dialysis or conservative therapy supported by a palliative treatment affects a large number of older adults, their families and health resources.

Recent evidence suggests that many patients over the age of 75, with more comorbidities, have a life expectancy and quality of life considerably low in dialysis (26-27).

Some studies have suggested an equal survival of older adults with multiple comorbidities, or poor physical functions, on conservative and on dialysis treatment, while other authors reported even a longer survival with palliative therapy (28–30).

Moreover, older adults on replacement therapy, have different needs than younger patients, so could be indicated a personalized replacement therapy (31), as home dialysis or assisted peritoneal dialysis.

The selection of the most appropriate options should comply with the individual needs, considering various aspects such as the patient’s choice, his/her psychological and clinical status, the social and family context, with a nephrological, geriatric and psychological team, which aims not only to prolong life expectancy, but also to improve the quality of life.

The Planning Preventive Care (PCP) is a process of discussion between an individual and his doctor regarding the concerns, the goals, the preferences, the prognosis and future therapy (32-33).

Therefore, it’s essential to correctly inform the patient and his family about the prognosis, the life expectancy, the quality of life, the risks, the benefits and the responsibilities of the offered therapy.

Conservative-palliative therapy provide a careful patient care, managing anemia, metabolic acidosis, hypertension and controlling fluids balance, symptoms such as pain, mental health problems, as depression, always considering the spiritual needs of the patient; indeed, spirituality and faith play an important role in doctor-patient relationship, and for the quality of life, by ensuring a good “end of life”, often through collaboration between nephrologists and palliativists in structures called “hospice” (34-36).

The prognostic knowledge of the outcome in older adult patients can influence treatment decisions, but often it mainly depends on the personal nature of clinical judgment.

A prognostic tool, currently used, is based on the presence of five variables such as age, dementia, peripheral vascular disease, decreased albumin concentration and the answer ‘no’ to the question ‘would you be surprised if the patient died in the next six months?’ (37).

Indexes such as the Multidimensional Prognostic Index (MPI) (38), which is a prognostic index of mortality in the short (1 month) and long-term (one year) based on information obtained from a Multidimensional Evaluation (VMD) of older adult (Table 2), have been developed during the last few years: classifying the risk of death of elderly patients in slight-middle-severe. The indexes considerably help the physician in such a difficult choice.

Neuro-psycho-cognitive disorders

Psychological and cognitive deficits are an important problem detected in older adult, with an increasingly high prevalence in CKD patients...
on conservative or replacement therapy (30-80% in HD patients) (39), although they’re often underdiagnosed.

The clinical picture is characterized by an executive and motoric decline and mnemonic, linguistic and cognitive deficits; it is attributed to brain's white matter diseases, to often clinically silent, cerebral infarctions (42), and typical hematohemical, acid–base homeostasis and hydroelectrolytic modifications (43).

Cognitive impairment can affect treatment adherence, by affecting the efficiency of daily activities, such as the proper intake of medications and diet, and it’s a significant prognosis factor for high morbidity and mortality in dialysis patients.

Moreover, CKD patients have a higher rate of psychological disorders, including depression associated with Vitamin D deficiency and with an inflammatory pathogenesis (44). These diseases greatly reduce the quality of life and have a negative impact on patient compliance, on clinical outcome and therefore on health care costs (45). Furthermore, in current clinical practice, we evaluate the survival but also the general health status and satisfaction towards the therapy, that allows a good patient compliance in addition to a considerable decrease of national health costs. For this reason it may be important to evaluate cognitive abilities, the psychological state of health and quality of life of older adult patients with CKD by giving them diagnostic

### Table 2 - Multidimensional Prognostic Index (MPI). Shortening: MDE, Multidimensional Evaluation

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<tr>
<th>The MPI is calculated by parameters that assess the following eight domains of the MDE:</th>
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<tbody>
<tr>
<td>1. Activities of Daily Living (ADL)</td>
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<tr>
<td>2. Instrumental Activities of Daily Living (IADL)</td>
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<tr>
<td>3. Short Portable Mental Status Questionnaire (SPMSQ)</td>
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<td>4. Mini Nutritional Assessment (MNA)</td>
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<td>5. Exton-Smith scale</td>
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<td>6. Comorbidity Index Rating Scale (CIRS)</td>
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<td>7. Number of medicines</td>
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<td>8. Living status</td>
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### Table 3. Psycho-diagnostic tests for the assessment of the neuro-psycho-cognitive status and life quality

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<tr>
<th>NEURO-PsyCHO-COGNITIVE TESTS</th>
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<tr>
<td>EVALUATION OF COGNITIVE ABILITIES</td>
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<tr>
<td>Montreal Cognitive Assessment (MoCA):</td>
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<td>The MoCA was created to make a fast screening of cognitive abilities' degeneration. It studies different cognitive fields: attention and concentration, executive functions, memory, language, visual-constructive abilities, abstraction, calculation and orientation. MoCA administration's time is 10 min. The maximum grade is 30 points; a result from 26 to 30 is considered normal.</td>
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<tr>
<td>Mini-Mental State Examination (MMSE):</td>
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<td>MMSE is a test used for the assessment of intelligence production's disorders and of cognitive abilities' degeneration. MMSE is used as a screening test to evaluate neuro-psycho-cognitive diseases in elderly patients with CKD. The test consists of 30 items, that refer to seven different cognitive zones: time orientation, space orientation, recording of words, attention and calculation, memory, speech, constructional praxis.</td>
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<tr>
<td>EVALUATION OF LIFE QUALITY AND HEALTH STATUS</td>
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<tr>
<td>Short Form 36 HealthSurvey (SF-36)</td>
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<td>SF-36 is a questionnaire on patients’ health condition that is characterized by shortness (on average the subject invests not more than ten minutes for its compilation) and by precision (the test is efficient and reproducible). The questionnaire SF-36 can be self-completed, or it can be an interview both by telephone or face to face.</td>
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<tr>
<td>ASSESSMENT OF THE PSYCHOLOGICAL STATUS</td>
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<tr>
<td>Geriatric Depression Scale (GDS)</td>
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<td>GDS is one of the most common scale for the assessment of depressive symptoms in elderly patients, but can be used also in patients suffering from soft-moderate dementia. It consists of 30 elements that exclude somatic and psychotic symptoms. There are &quot;yes or no&quot; answers and this makes it particularly appropriate for elderly patients with cognitive disorders. The result can vary from 0 (not depressed) to 30 (several depression), with a threshold of 11; if the results are higher than 11 it means that depressive symptoms are clinically relevant.</td>
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</table>
tests, such as the Mini-Mental State Examination (MMSE) (46), the Montreal Cognitive Assessment (MoCA) (47), the Geriatric Depression Scale (GDS) (48) and the Short Form 36 Health Survey (SF-36) (Table 3), with a multidisciplinary management by a team of geriatricians, neurologists, psychologists or psychiatrists.

Kidney transplantation in elderly patients

Kidney transplant is the first-line treatment for patients with ERSD, often even in older adult patients, and even if the number of patients with ERSD is constantly increasing, the total number of kidney transplants remains almost the same (49). In the most recent years, as a result of a permanent lack of organs and with a lot of rejected organs, we’ve tried to extend the age of donors and the age of receiving patients using the donation of marginal organs and through the procedure of double kidneys transplant in order to optimize the outcome (50). For this reason kidneys that are normally rejected have been used for transplants: transplant from dead donors, donors without heartbeat, marginal donors like elderly people, people suffering from high-blood pressure, diabetics, overweight people, people suffering from kidney stones or living donors with a diagnosis of malignant tumor, people with potential and contagious infections or suffering from kidney cysts (51). The Senior Program Eurotransplant (52) is an “old to old” system of allocation, highlighting the importance of keeping the time of ischemia short at a low temperature and of innovative techniques of conservation and allocation. The most common problems of non-optimal kidneys transplants are a delayed recover of organ functionality and the transplant failure in the short or long term, even if the first long term results show the same survival rate in both patient and transplanted organ as in non-marginal transplants. This is true only if an appropriate and standardized pre-transplant biophtical (52-53) valuation is done, reducing the waiting lists.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The manuscript has been seen and approved by all authors. This study was not funded. The manuscript is not under consideration for publication elsewhere.

References

36. Lucchetti G, Almeida LG, Granero AL et al. [Spirituality for dialysis patients: should the nephrologist address?]. Jornal brasileiro de nefrologia : 'orgaoo-


Corrispondenza
Silvia Lai
e-mail: silvia.lai@uniroma1.it