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Review Article

Predialysis Care and Timing of Dialysis Initiation: A Crucial Issue for Patient and Nephrologist

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Abstract

The transition from an advanced stage of chronic kidney disease to the regular dialysis treatment is a crucial moment not only for the patient but also for the nephrologist who is responsible for assessing when the most suitable time to start renal replacement therapy is and what the most appropriate way for the individual patient is.

To achieve this, it is important to take early care of the patient by the nephrologist, preferably if assisted by other health figures to set up multidisciplinary teams in outpatient clinics dedicated to predialysis care to slow the progression of chronic renal damage and to obtain better results in terms of survival and others clinical outcomes in the subsequent phase of the renal replacement therapy.

Another important aim of an early approach to the patient with chronic kidney disease is to reduce the percentage of late referral that represents an independent risk factor for early death on dialysis, especially for elderly patients.

Despite the many studies carried out so far, it is still not clear what the most suitable time to start dialysis is. Even the major international guidelines had to adapt to the indications that emerged from such a wealth of studies by sharing the concept that it is not only the estimate of the glomerular filtrate that guides the start of dialysis but a set of clinical, social and aptitude assessments, focused on the patient as a whole. To reach such conclusions, it is necessary to have a series of data and knowledge that only an early and careful predialysis care can offer.

ABBREVATIONS

GFR: Glomerular Filtration Rate; CKD: Chronic Kidney Disease; PNC: National Chronicity Plan; RRT: Renal Replacement Therapy; MaReA: Advanced Renal Disease; ESRD: End Stage Renal Disease

INTRODUCTION

Chronic Kidney Disease (CKD) is an important cause of morbidity and mortality and makes up for a relevant problem of public health [1-3]. The interest toward CKD derives, aside from its diffusion, from the realization that it is preventable with the adequate measures of primary, secondary and tertiary prevention [4,5].

CKD is constantly increasing mainly due to an ageing general population and evolves in its end-stages towards renal replacement therapy (RRT). In Italy it is estimated that 8-10% of the population is affected by CKD to various degrees of gravity [6].

Recently, in Italy, the Health Ministry enacted the National Chronicity Plan (PNC) in which CKD was included in the 10 chronic illnesses that need special attention [7]. One of the major objectives of PNC, aside from incentivizing kidney transplants, was the personalization of dialysis therapy and keeping the patient at home. This strategy makes it easier for the patient to return to everyday life and work and improves quality of life while reducing costs.

To reach these objectives, it is fundamental to have an early referral of the CKD patient to a dedicated multidisciplinary outpatient setting that can counseling patients (and preferably also their families) on a path that starts from the first phases of renal failure to terminal ones where RRT becomes essential.

These last steps can be identified as the transition period from an advanced CKD state to a definitive RRT and make up for a crucial moment not only for the patient but for the nephrologists as well, who has to evaluate the best moment to start RRT, and also what the best way is for each individual patient. Several scenarios arise in this phase and a different approach needs to

be taken for each patient according to his condition [8]: going from CKD to dialysis, from CKD to kidney transplant, going back to dialysis after transplant, conservative therapy continuation based on a diet and recourse to palliative care.

To this day, there is no precise data on the exact timing for when to begin dialysis. The IDEAL study - the only randomized trial carried out on this topic to this day - has not shown any significative differences of survival and other secondary outcomes in the two patient groups that started dialysis at different stages of residual kidney function [9].

Even after this study, the latest guidelines of the various nephrological societies suggest that the beginning of dialysis should not be driven by Glomerular Filtration Rate (GFR) alone but also by a careful global evaluation of the patient mainly directed at finding uremic signs and symptoms.

PREDIALYSIS NEPHROLOGY CARE

It is a common opinion that early referral to a nephrologist and proper patient education are essential and complementary for better survival and other important clinical outcomes [10-14].

The early referral of patient with CKD at risk of End-Stage Renal Disease (ESRD) to a nephrologist makes it possible to implement all procedures and treatments to control the progression of the disease. Such procedures include tight control of blood pressure, use of drugs that inhibit renin-angiotensin system, lifestyle changes (exercise, quitting smoking etc.), low-protein diet, use of statins and optimal glycemic control in diabetic patients. An early reference to the nephrologist can also prevent complications of CKD such as malnutrition, anemia, osteodystrophy and acidosis that occur in early stages of renal failure [15]. It also facilitates an opportunity to intervene on other relevant important prior to comorbidities such as cardiovascular disease and neuropathy and also to better prepare patients for dialysis through an educational program [16-17]. The beginning of hemodialysis treatment must be scheduled within the required time and with an existing vascular access. Patient education is crucial because it increases awareness of the disease and treatment modalities to determine collaboration between patient and medical staff in terms of compliance and timely reporting of problems. The inclusion in an outpatient program also seems to improve the rehabilitation and quality of life [18,19].

This approach requires an early identification of a patient with CKD. Unfortunately, more often, the nephropathic patient comes to the attention of a nephrologist in advanced stages of the disease or when an RRT will be needed soon. In some places, the blood creatinine measurement, which is required for the evaluation of renal function is- prescribed only in 20% of patients at risk of ESRD (elderly, hypertensive, diabetic) [20]; this low frequency reflects the inadequate attention of general practitioners about kidney disease and consequently the difficulty in identifying early-stage patients with renal failure

In addition to the early recognition of the nephropathic subject it is essential that the terminology of renal failure is standardized and disease is classified according to the K/DOQI stages. Creatinine values alone should not be used to establish the level of kidney function and lately the calculation of the glomerular filtrate under the CKD-EPI formula seems to better react to these needs [21-22].

The late sending of a patient to a nephrologist (late referral) is an independent risk factor for early death or requiring dialysis [23]. Elderly patients are often referred late to nephrologists and likewise begin dialysis with a temporary access; starting dialysis with a temporary catheter increases the risk of death [24]. Unfortunately, a good percentage of patients treated at the outpatient clinics start dialysis in an emergency due to inappropriate planning of dialysis or of creating vascular access [25]. Therefore it is very important to give the patients access to a clinic dedicated to pre-dialysis where not only nurses and doctors, but also dietitians, and psychologists etc. are able to provide the necessary information and collaborate in planning the start time of dialysis. A patient treated in a multidisciplinary pre-dialysis clinic has fewer hospitalizations and has a better chance to start dialysis with a permanent vascular access in addition to a significantly higher survival rate, compared to a patient in an outpatient standard clinic.

It is well known that in some parts of the world patients are more often informed about hemodialysis compared to peritoneal dialysis or transplantation, and this affects the subsequent treatment modalities penalizing the choice of peritoneal dialysis [26].

Another important point is that CKD patients should be promptly addressed to nephrology centers who will be responsible for dialysis treatment. This will allow an opportunity to maintain continuity of treatment as much as possible in different phases of the disease, particularly in the delicate start-up to the dialysis.

A recent review confirmed the importance of education in patients to allow for an informed decision-making process regarding the options of dialysis. However, there is a lack of clinical trials data on the most efficient education method and on the competencies of the specialized personnel to develop it. It is then necessary to have a standardized approach based on the best evidence given by CKD and by other clinical conditions to guarantee the validation of pre-dialysis education programs and their effects on the clinical results and on the treatment choices [27].

It is interesting to point out the experience of Piedmont, the North-Western Region of Italy (4,356,406 inhabitants), covering an area of almost 29,000 km^2 where, by 31 Dec 2018, 5636 patients are presently receiving RRT: 2813 are on hemodialysis, 374 on peritoneal dialysis and 2449 have a functioning kidney graft [28]. In 2013 a regional resolution has established the MaReA clinic (Italian acronym for Advanced Renal Disease) in each of the Nephrology and Dialysis Units of Piedmont to make homogeneous the CKD prevention process, diagnosis and care of patients with a glomerular filtrate less than 30ml/min including patients that received a transplant with a similar decline in kidney function and the start of RRT [29].

One of the features of this clinic is the multidisciplinary approach that makes it possible for the nephrologist, the main figure, to share the patient's therapy with nurses, dietitians and psychologists.

- To this end, the medical clinic is mainly aimed at:Preventing the evolution of kidney disease delaying the course to RRT.
- Reducing the complications linked to uremia and the necessity of hospitalization and delaying the start of urgent dialytic treatment.
- Activating a homogeneous process of RRT choice that allows to incentivize, for eligible patients, both the transplant from living or cadaver (preventive or after the start of dialysis) and home dialysis.
- Giving the option of a conservative therapy as an alternative to dialysis for patients that refuse the dialytic treatment and for those in very advanced age with grave comorbidities.

One of the strengths of the MaReA clinic is the definition of a path of choice for home dialysis treatments as a "bridge" for kidney transplants. Another peculiarity of this clinic is to establish which is the treatment with the best impact on quality of life or the lowest social cost for the remaining patients not suitable for kidney transplantation. In this context, extreme conservative therapies such as highly hypoprotein diets supplemented by keto-analogues and, in selected cases, palliative therapy may find space.

Despite this strategy, in 2018 the percentage of late referral patients undergoing dialysis in Piedmont was about 30%, a substantially stable figure but still high even if lower than the literature cases in which the average is around 40-60% [17,24]. This data shows that much work still needs to be done on the path of interception of patients with CKD in early stages in collaboration with local services and general practitioners. Moreover there is a need to better and more homogeneously define the criteria of a late referral patient.

TIMING OF DIALYSIS INITIATION

The ideal time to definitively begin dialysis treatment in patients with ESRD has not yet been well defined. The transition period to dialysis presents an exceptionally high frailty condition for patients: the annual mortality rate in CKD, stage 5, during the first year of dialysis in fact exceeds 20% [30]. The results of the IDEAL study on early and late initiation of dialysis, the only randomized trial that tested the impact of initiating dialysis at two different levels of renal function on outcomes, showed no significant difference in survival or other patient centered outcomes [9].

The IDEAL study was conducted between July 2000 and November 2008, and enrolled a total of 828 adults with progressive advanced CKD, defined as an eGFR (calculated by the Cockcroft-Gault equation) of 15 ml/min/1.73 m^2 of body surface area. Patients were recruited at 32 centers in Australia and New Zealand and were randomized to initiate dialysis at an eGFR of 10-15 ml/min/1.73 m^2 (termed "early start") or when the eGFR had fallen to 5-7 ml/min/1.73m^2 (termed "late start"). The landmark primary finding in the primary report from the IDEAL study was that there was no significant difference between the study groups in all-cause mortality, or in any clinically important secondary outcome, including hospitalizations and cardiovascular events. There were additionally no substantial differences between the study groups in health-related quality of life, as measured by the well-validated SF-36 survey instrument.

This data thus questioned the consolidated paradigm of the use of glomerular filtration estimates as the main guide for initiating dialysis and suggested the need to investigate what other aspects can be useful for optimizing the transition period from CKD to dialysis.

In the years following the publication of the IDEAL study, a large number of observational studies based on large databases were conducted to explore the various aspects regarding the correct timing of the start of dialysis [31-35].

Taken together, these studies suggest that despite the many limitations of observational studies due to confounding elements and selection bias, there is no convincing evidence that initiating dialysis with a high or low eGFR, as defined by the IDEAL study, has a substantial impact on patient outcomes. Furthermore, these studies raise the question of whether initiating dialysis at even lower levels of glomerular filtration function can be safe, if not beneficial, for patients.

Even the guidelines of the most important international nephrological societies had to adapt to the indications that emerged from such a wealth of studies (Table 1) [36-40]. The impression is that the concept that it is not only the estimation of the glomerular filtrate that guides the initiation of dialysis but a set of clinical and even socio-aptitude assessments is widely accepted. It is also confirmed that, compared to the last decades, where the indications emerged from urea kinetics studies were still influential and that they recommended the start of dialysis treatment at generally high GFR values (10-15 ml/min), in the last years the limit has been moved towards lower values of filtrate, as demonstrated in clinical practice by the large North American case studies. According to the USRDS registry, the percent of incident ESRD patients who started dialysis with GFR ≥10 ml/min/1.73m^2, which had previously risen from 13% in 1996 to 43% in 2010, fell slightly to 40% in 2013. Similarly, the percentage of incident dialysis patients who initiated RRT with GFR <5 ml/min/1.73m^2, which had previously fallen from 34% in 1996 to 12% in 2010, rose to 14% in 2013 [30].

Taken together, this evolution of the guidelines on timing of initiation of dialysis over the past 10 years shows a profound influence of the results of the IDEAL study and those of the most recent observational studies that suggest benefits or even harm associated with initiating dialysis at levels higher than the lower levels of kidney function.

Furthermore, there is a clear tendency to focus on the evaluation of symptoms/signs of uremia and on the decision-making process shared between nephrologists, patients and other health figures as well highlighted by Wong's recent work [41]. In this qualitative study, Wong and colleagues tried to identify the central issues related to the timing of the start of dialysis by carrying out a qualitative analysis of the medical records of almost 1700 patients who started dialysis in the Veteran Affair system from 2000 to 2009.

Table 1: Timing of dialysis initiation according to the major international guidelines based on the latest updates.

Guide Lines	GFR	Comment
KDOQI (2015) [34]	not indicated	The decision to initiate maintenance dialysis in patients who choose it should be based primarily on an evaluation of the signs and/or symptoms associated with uremia, malnutrition and the ability to safely manage metabolic abnormalities and / or volume overload with medical therapy rather than at a specific level of kidney function in the absence of such signs and symptoms
KDIGO (2012) [35]	Caution when GFR <10-5 ml/ min	Suggests starting dialysis in the presence of one or more of the following conditions: symptoms or signs related to kidney failure [acid-base or electrolyte abnormalities, itching]; inability to control volume or blood pressure; a progressive deterioration of the nutritional state refractory to dietary intervention or cognitive impairment. This occurs often but not invariably in the GFR range between 5 and 10 ml/min/1.73 m^2. (2B)
ERA-EDTA/ERBP Advisory Board (2011) [36]	Caution when GFR <9-6 ml/min	In patients with GFR <15 ml/min/1.73 m^2, dialysis should be considered in the presence of one or more of the following conditions: symptoms or signs of uremia, inability to control hydration status or blood pressure or a progressive deterioration of the nutritional status. It should be borne in mind that most patients will be symptomatic and will have to start dialysis with GFR in the range 9-6 ml/ min/1.73 m^2. High risk patients, e.g. diabetics and those whose kidney function is deteriorating faster than eGFR 4 ml/min/year require particularly careful supervision. Asymptomatic patients with advanced CKD may benefit from a delay in initiating dialysis in order to allow for the preparation, planning and creation of permanent access rather than the use of temporary access
Canadian Society of Nephrology (2014) [37]	GFR<6 ml/min	For adults (aged> 18 years) with an eGFR of less than 15 ml/min per 1.73 m^2, an "intent to defer" approach is recommended over an "intent to start" approach. Patients with an eGFR of less than 15 ml/min per 1.73 m^2 are closely monitored by a nephrologist and dialysis is initiated with the first onset of a clinical indication or a decline in the eGFR at 6 ml/min per 1.73 m^2 or less, whichever comes first. Clinical indications for initiating dialysis include: symptoms of uremia, fluid overload, refractory hyperkalaemia or acidemia or other conditions or symptoms that can be improved by dialysis. In the absence of these factors, eGFR should not serve as the sole criterion for initiating dialysis unless it is 6 ml/min per 1.73 m^2 or less.
UK Renal Association (2009) [38]	GFR<6 ml/min	The decision to initiate RRT in CKD stage 5 patients should be based on careful discussion with the patient of the risks and benefits of RRT taking into account the patient's symptoms and signs of renal failure. Dialysis initiation should be seriously considered when the eGFR is less than 6 ml/min/1.73 m^2, even if the patient is asymptomatic.

Abbreviations: GFR: Glomerular Filtration Rate; CKD: Chronic Kidney Disease; RRT: Renal Replacement Therapy

This analysis revealed the extraordinary complexity and great variability of the elements affecting the decision to initiate dialysis by clinicians, patients and their families. In particular, investigators found that the timing decision on the initiation of dialysis often revealed underlying tensions and differences between the doctor's priorities and the patient/caregiver's goals and preferences. Studies such as this emphasize the challenges of implementing guidelines in real clinical practice and highlight the need for a greater understanding of how to customize and target interventions such as initiating dialysis according to the needs of each individual patient.

There is, therefore, the perception that the future development of the guidelines and recommendations relating to clinical practice will depend on the investments in future research work to define the physiological and biological basis of the uremic syndrome, identify which uremic signs and symptoms improve reliably with the initiation of dialysis and determine how the assessment of the load of uremic symptoms can be systematically and effectively integrated into meetings between clinicians and patients.

Finally, an interesting aspect of the research is that a group of biological markers such as protein-bound solutes (indoxyl sulfate, p-cresyl sulfate and hippurate), produced by the intestinal microbial flora, and could potentially help in the decision-making process of initiating dialysis. Their accumulation during renal failure has been associated with the progression of chronic kidney disease and cardiovascular mortality [42]. Moreover both indoxyl sulfate and p-cresyl sulfate have been associated to fatigue, uremic pruritus, anorexia and other symptoms of uremic syndrome [43].

However, future research could suggest additional biological markers for potential integration into a new clinical paradigm for decision making in dialysis.

CONCLUSION

The transition period from an advanced CKD state to the definitive dialysis treatment phase is a crucial moment not only for the patient but also for the nephrologist who is responsible for assessing when the most suitable time to start replacement therapy is and what the most appropriate way for the individual patient is; in fact, several scenarios appear at this stage and for each of them there has to be an approach centered primarily on the patient.

This is why it is important to take early care of the patient by the nephrologist, preferably if assisted by other health figures to set up multidisciplinary teams, in outpatient clinics dedicated to predialysis. Although there is a need to standardize educational programs in this area, correct and careful patient care in the predialytic phase allows to slow the progression of chronic renal damage and to obtain better results in terms of survival and secondary clinical outcomes in the subsequent phase of the replacement treatment.

However, one of the future objectives is to reduce the percentage of late referral patients who initiate replacement

treatment as this condition represents an independent risk factor for early death on dialysis, especially for elderly patients.

Despite the many studies carried out so far, it is still not clear when the most suitable time to start dialysis is; the IDEAL study, the only randomized trial currently, which tested the impact of initiating dialysis at two different levels of renal function on survival and other clinical outcomes, did not demonstrate significant differences between the two groups of patients. Even the major international guidelines had to adapt to the indications that emerged from such a wealth of studies by sharing the concept that it is not only the estimate of the glomerular filtrate that guides the start of dialysis but a set of clinical, social and aptitude assessments, focused on the patient as a whole, and it is obvious that in order to reach such conclusions it is necessary to have a series of data and knowledge that only an early and lasting predialysis care can offer.

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