J Nephrol (2016) 29:153–161
DOI 10.1007/s40620-015-0243-8

REVIEW

Stage 5-CKD under nephrology care: to dialyze or not to dialyze, that is the question

Mario Pacilio[1] · Roberto Minutolo[1] · Carlo Garofalo[1] · Maria Elena Liberti[1] · Giuseppe Conte[1] · Luca De Nicola[1]

Received: 7 September 2015 / Accepted: 24 October 2015 / Published online: 19 November 2015

Abstract Appropriate timing of starting chronic dialysis in patients with advanced chronic kidney disease (CKD) under nephrology care still is undefined. We systematically reviewed the most recent studies that have compared outcomes of stage 5-CKD under conservative versus substitutive treatment. Eleven studies, most in elderly patients, were identified. Results indicate no advantage of dialysis over conservative management in terms of survival, hospitalization or quality of life. This information is integrated with a case report on a middle-aged CKD patient followed in our clinic who has remained for 15 years in stage 5 despite severe disease. The patient is a diabetic woman who underwent right nephrectomy in 1994 because of renal tuberculosis. In 1999, she commenced regular nephrology care in our clinic and, since 2000, when she was 53 years old, her estimated glomerular filtration rate (eGFR) has been $\leq$15 ml/min/1.73 m^2. Over the last decade, despite, several episodes of acute kidney injury and placement of permanent percutaneous nephrostomy in 2001, renal function has remained remarkably stable, though severely impaired (eGFR 7.7–5.6 ml/min/1.73 m^2). Our systematic analysis of the literature and this case report highlight the need for further studies, not limited exclusively to elderly patients, to verify the efficacy of non-dialysis treatment in stage 5-CKD patients. Meanwhile, nephrologists may consider that their intervention can safely prolong for several years the dialysis-free condition in ESRD independently of age.

Keywords CKD · Systematic review · Case report · Diabetic kidney disease · Proteinuria · Nephrology care

Introduction

In chronic kidney disease (CKD), when the glomerular filtration rate (GFR) approaches the level of 15 ml/min/1.73 m^2 [stage 5 or end-stage renal disease (ESRD)], nephrologists face the difficult choice between starting renal replacement therapy (RRT) or prolonging conservative therapy. RRT represents, at least in higher- or middle-income countries, the "easy and safe" choice; however, consensus is now growing on conservative management (CM) as a treatment alternative to RRT in ESRD [1].

The recent KDIGO Controversies Conference on Supportive Care in CKD identified conservative therapy as a priority for improving patient-centered care [2]. Indeed, the opinion of the Conferees on the best treatment for ESRD—whether CM or RRT—was far from unanimous, with some claiming that RRT improves survival in the large majority of patients while others stated that it may offer limited, if any, benefit in terms of survival or quality of life. Similarly, in a survey among European nephrologists on the decision-making process, while level of renal function emerged as the most important factor in uncomplicated patients, several other factors were reported as needing to be taken into account in the population at large [3]. Therefore, more studies are needed to help clarify decision-making about when CM is still appropriate in ESRD [2, 4].

We performed a systematic review of studies published in the last decade comparing the main clinical outcomes of

Electronic supplementary material The online version of this article (doi:10.1007/s40620-015-0243-8) contains supplementary material, which is available to authorized users.

✉ Luca De Nicola
luca.denicola@unina2.it

[1] Nephrology Division, Second University of Naples-Med School, S.M.d.P Incurabili Hospital, Via Maria Longo 50, 80138 Naples, Italy

stage 5-CKD patients under CM versus RRT. The aim of this analysis was to expand knowledge on the best treatment of ESRD, given the low number of studies published on this issue and the fact that only one systematic analysis is available in the field (though not specifically aimed at comparing CM versus RRT in ESRD and, moreover, updated only to 2011) [5]. The information derived from the systematic analysis was integrated with a case report of a patient from our outpatient clinic with a prolonged course of non-dialysis stage 5-CKD.

Systematic review

Methods

We searched published studies comparing clinical outcomes, i.e. rates of survival, hospitalization, and quality of life, in stage 5-CKD patients under conservative versus dialysis therapy. A systematic search of articles published in all languages was performed using PubMed, including Medline, Scopus and Web of Sciences databases, to identify relevant studies published in the last decade (January 2005 to September 2015). We used the following medical subject headings (MeSH) and text words: "nondialytic", "non-dialytic", "conservative management", "conservative", "conservatively" and "chronic kidney failure", "chronic renal failure", "end-stage renal disease", "end-stage kidney disease", "end-stage renal failure", "stage 5 CKD", and "advanced CKD". The detailed search syntax is reported in Appendix (Item S1). Bibliographies of relevant articles and reviews were also manually screened for additional studies.

Original studies, either randomized or observational, comparing conservative versus dialysis treatment in stage 5-CKD, were retained; studies were excluded if sample size was less than 50 patients and/or no data on the outcomes of interest were provided. The search was designed and performed by one author (CG) under the supervision of two senior authors (GC and LDN).

Results

A flow diagram of the selection process is presented in Fig. 1. Eleven studies were finally considered for analysis (Table 1).

We found only two randomized clinical trials (RCT). The Diet Or Dialysis in the Elderly (DODE) was a multicenter trial in Italy showing that a supplemented very low protein diet (0.3 g/kg body weight) can safely postpone dialysis treatment for about one year in elderly patients (aged $>$ 70 years) with very low GFR (5–7 ml/min/1.73 m^2) [6]. The main limitations were exclusion of diabetics and incomplete enrollment that reduced the statistical power of analysis. The other study, Initiating Dialysis Early and Late (IDEAL), enrolled quite a large number of adult patients (mean age 60 $\pm$ 12 years) to compare outcome of early versus late dialysis start [7]. Results showed that dialysis may be safely delayed with careful clinical management. However, 19 % of subjects of the "early start" group commenced dialysis later while 76 % of "late start" subjects started early. Hence, the difference in eGFR at the time of initiation of dialysis was smaller than originally planned (eGFR: 9.0 and 7.8 ml/min/1.73 m^2 in the early and late group, respectively), and the median difference in time to dialysis initiation was only 5.6 months. Of note, the vast majority of patients had been seen by the nephrologist for about 10 months before enrollment; IDEAL patients in fact appeared well nourished and well prepared, with an extraordinarily high percentage (60 %) starting RRT by peritoneal dialysis (PD) modality.

The nine observational studies included elderly patients in the vast majority of cases, with patients under conservative treatment being of a consistently higher age compared to the dialysis group [8–16]. Besides the advanced age, these studies had major methodological drawbacks. A complete description of essential basal features, such as prevalence of diabetes and cardiovascular disease (CVD), was in fact provided in only two studies [14, 15]. Furthermore, most (n = 7) studies had a retrospective design [8–10, 13–16]. Finally, follow-up was generally short with only three studies having a median value longer than 4 years [9, 10, 15]. In interpreting the results of these studies, therefore, these methodological pitfalls should be borne in mind.

The retrospective study by Carson et al. showed that dialysis prolongs survival by approximately 2 years in elderly patients who have ESRD and significant comorbidities [9]; however, this result was obtained in a small CKD population that started hemodialysis (HD) after only short-term (<3 months) or no nephrology care in almost half of the cases, and, more important, survival analyses were not adjusted for potential confounders. Conversely, two studies with adequate sample size and a longer follow-up did not confirm the superiority of RRT over CM in fully adjusted analyses [10, 15].

The importance of adjusting for comorbidities further emerges in the study by Murtagh et al. [8]. This study showed that in patients over 75 years of age, and who received nephrology care early, the survival advantage of dialysis was significant, with a 2-year survival rate of 76 versus 47 % in dialysis and CM, respectively; however, the survival advantage was lost in patients with high comorbidity scores, particularly those with ischemic heart disease. Similarly, in the study by Hussain et al. [13], RRT showed a survival advantage over CM but, again, as age

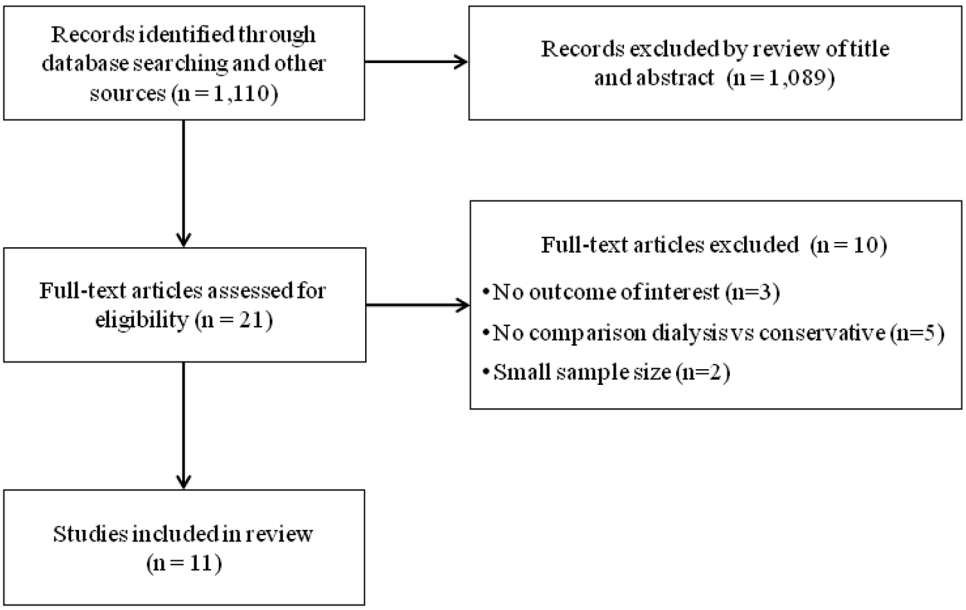

Fig. 1 Flow diagram of the literature selection process

and co-morbidity burden increased and performance status deteriorated, dialysis lost its survival advantage. Of note, RRT patients were also more frequently admitted acutely to, and died in, hospital [13]. A recent study by Shih et al. confirmed that age is a potent modifier of the association between dialysis therapy and mortality risk [16]. The authors evaluated a large population (>8000 patients aged ≥70 years) with advanced CKD (eGFR < 15 ml/min/1.73 m^2) treated either conservatively or dialyzed. They found that dialysis therapy was associated with a 40 % higher mortality risk compared to conservative care [adjusted hazard ratio (HR) 1.39, 95 % confidence interval (CI) 1.30–1.49] [16]; in subgroup analyses, moreover, the mortality risk in dialysis remained consistently increased, independently of sex, comorbidities and even age.

The major role of disease severity in modifying prognosis of dialysis-treated patients was found by Shum et al. when comparing CM vs. peritoneal dialysis [14]; they found that the survival advantage of dialysis was preserved in patients receiving PD with low comorbidity but was lost in those with high comorbidity. Similarly, Da Silva et al. showed that mortality risk in the dialysis group was approximately half that in CM patients [HR 0.47 (0.20–1.10); p = 0.08] but the difference was less in patients with high comorbidity score [11]. As for survival, also health-related quality of life seems not to improve in dialysis-treated ESRD patients who are elderly or have a high comorbidity burden [12].

Comments

The progressive nature of CKD has always been a key research focus in Nephrology [17, 18]. In 1991, Maschio et al. hypothesized the existence of a 'point of no return', corresponding to a residual GFR of about 50 ml/min beyond which progressive worsening of renal function is considered irreversible and poorly responsive to any nephroprotective intervention [19]. Recent studies have challenged this traditional view by revealing different rates of GFR decline in CKD of similar severity, with some patients experiencing a rapid progression to RRT and others maintaining stable renal function over time independently of the disease stage [20]. Indeed, non-progressive CKD is typically encountered in the subgroup of older non-diabetic patients with low proteinuria and mild to moderate disease (CKD stage 1–3) [21–26]; nonetheless, non-progressors have been identified, though less frequently, in more advanced CKD [27–30]. The recent paradigm shift on the "equivalence" between CKD and unrelentless decline of GFR is, at least in part, dependent on the wider implementation of preventive nephrology care with its multifaceted therapeutic armamentarium aimed at limiting progression to RRT and mortality [31–34].

The persistent, and critical, dilemma mainly derives from the absence of solid evidence-based studies on this issue. Previous observational single-arm studies have shown that conservative care by the nephrologist can prolong for 6–24 months the dialysis-free condition safely and with satisfactory quality of life, in patients with stage 5-CKD [1, 5, 35–39]. Patients included in these studies were mostly over 75 years of age; the only exception was the study by Di Micco et al. in 30 middle-aged patients (55.7 ± 13.4 years) [37] showing that nephrology care was associated with a median time of 11.8 months from eGFR ≤ 11.0 ml/min/1.73 m^2 to dialysis. On the other hand, the validity of HD as an exclusive therapy for ESRD

Table 1 Studies in the last decade comparing outcomes of stage 5-CKD patients under conservative versus dialysis treatment

References	Design/setting	Outcome	Sample	Age (years)	eGFR	CVD (%)	DM (%)	FU (months)	Main findings
Randomized									
Brunori [6]	VLPD vs. dialysis in elderly	Mortality, hospitalization	VLPD: 56	79.3 ± 6.4	5–7	68[a]	None	27	VLPD postpones dialysis with no higher mortality or hospitalization
			Dialysis: 56	76.8 ± 4.3		60[a]			
Cooper [7]	Early vs. late dialysis start	Mortality, adverse events	Early: 404	60.2 ± 12.8	10–14	39.6[a]	42.6	43	Similar mortality and adverse event rates
			Late: 424	60.5 ± 12.3	5–7	38.2[a]	43.2		
Observational									
Murtagh [8]	Retrospective in elderly; CM vs. dialysis	Survival	CM: 77	83.0	<15	NA	25.0	24	In dialysis, survival advantage that is lost if high comorbidity
			Dialysis: 52	79.6			23.4		
Carson [9]	Retrospective; CM vs. dialysis	Survival and hospitalization	CM: 29	83	<10.8	NA	14.0	50	Unadjusted survival and hospitalization greater in HD
			HD: 173	75	NA		29.0		
Chandna [10]	Retrospective; CM vs. dialysis.	Survival	CM: 155	77.5 ± 7.6	13.2	NA	35.5	55	Adjusted survival similar in the two groups
			Dialysis: 689	58.5 ± 15.0	13.2		34.3		
Da Silva [11]	Prospective; CM vs. dialysis	Survival, quality of life	CM: 30	77.5 ± 6.5	13.3	NA	NA	36	Similar adjusted survival and quality of life
			HD: 80	60.6 ± 14.9	14.2				
			PD: 44	48.0 ± 15.6	14.3				
Seow [12]	Prospective; CM vs. dialysis in elderly or high comorbidity pts	Quality of life	CM: 63	78	10	NA	60.3	24	In dialysis quality of life not better in elderly and/or high comorbidity burden
			Dialysis: 38	71	10		84.2		
Hussain [13]	Retrospective; CM vs. dialysis in elderly	Survival	CM: 172	>70	<20	NA	NA	NA	In dialysis survival advantage lost for pts over 80 y or with high comorbidity
			Dialysis: 269						
Shum [14]	Retrospective; CM vs. PD in elderly	Survival, hospitalization	CM: 42	75.3 ± 5.7	6.8	75	67	24	In PD, lower hospitalization and longer survival, lost if comorbidity burden is high
			PD: 157	73.4 ± 5.3	6.3	71	53		
Crews [15]	Retrospective; early vs. late dialysis start	Survival	Early: 146	65.7 ± 13.7	≥10	50.1[b]	41.1	52	No difference in adjusted survival
			Late: 80	63.5 ± 15.4	<10	38.8[b]	50.0		
Shih [16]	Retrospective; CM vs. dialysis in elderly	Survival	CM: 2049	82.0 ± 6.4	<15	NA	35.1	32	Dialysis associated with shorter survival vs. CM
			Dialysis: 6292	78.6 ± 7.1			37.3		

Age is mean ± SE or median

VLPD very low protein diet, *CM* conservative management, *FU* months of follow-up (median), *eGFR* estimated GFR (ml/min/1.73 m^2) at start of follow-up for endpoint analysis, *CVD* cardiovascular disease including peripheral, cerebral vascular disease, and ischemic heart disease[a], or coronary artery disease, chronic heart disease and cerebrovascular disease[b], *HD* hemodialysis, *PD* peritoneal dialysis, *NA* not available

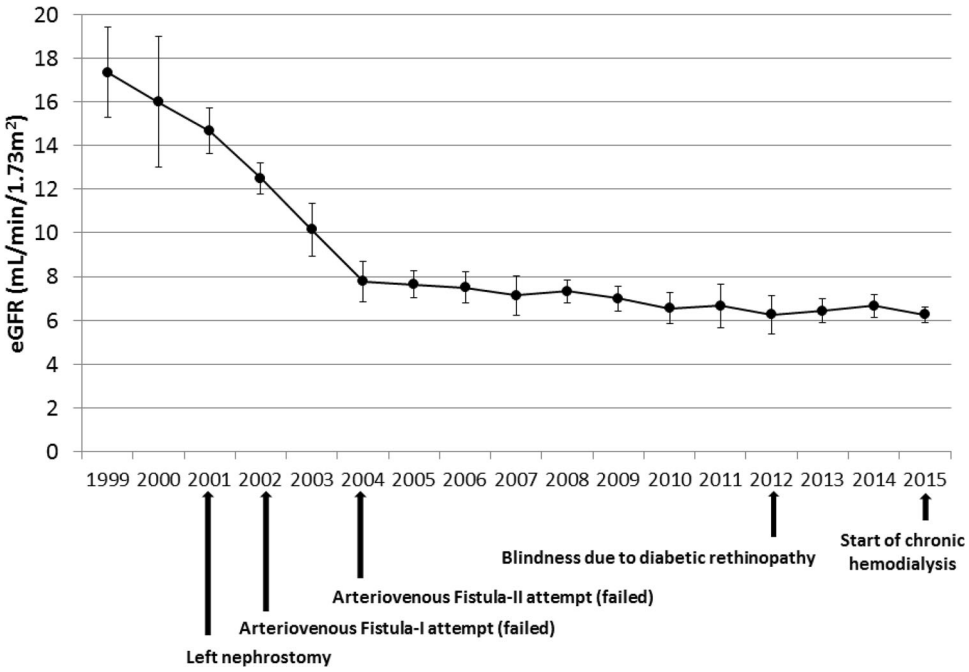

Fig. 2 MDRD-GFR and main events during nephrology follow up

for all patients has been confuted by a large study (n = 3702) in nursing home residents starting treatment in the United States (aged 73.4 ± 10.9 years, basal eGFR 10.7 ± 4.9 ml/min/1.73 m^2) [40]; the authors found that only 25 % survived and only 1/8 of survivors maintained functional status after the first year of dialysis.

Our systematic review, though limited by the search made by a single author, adds novel information on this issue by specifically examining, for the first time, the studies comparing outcomes of stage 5-CKD patients under RRT versus CM (Table 1). In interpreting the results of the studies, one should consider major drawbacks, including the highly selected study population with patients aged over 70 years in most cases. Overall, the studies do not indicate a superiority of dialysis, especially in the presence of older age and/or high comorbidity scores, in terms of survival or of quality of life. These findings therefore highlight the possibility of safely delaying RRT in advanced CKD by careful nephrology care in very ill patients as well as in those very old.

Case report

Our patient is a Caucasian woman born in 1947, with type 1 diabetes mellitus (DM1) diagnosed in 1974. In 1994, we transitorily followed her because of renal tuberculosis (TB)-induced obstructive acute kidney injury (AKI). Triple treatment of TB for 1 year allowed eGFR to recover to basal value within 6 months, as previously described [41]. At that time, the right kidney was surgically removed as gross cavities, in which the renal parenchyma was a thin shell, were documented. Subsequent controls to detect Mycobacterium in the urine were all negative while several bacterial urinary tract infections (UTIs) were diagnosed and treated.

In 1999, she was referred by the general practitioner (GP) to our clinic because of low eGFR (17.8 ml/min/1.73 m^2). Since then, the patient has been regularly followed in our outpatient clinic (Fig. 2), with several visits and biweekly-to-monthly phone contacts. Despite her low educational level (only primary school), the patient was efficaciously instructed as regards recognizing symptoms of UTI and volume depletion, and monitoring body weight and blood pressure (BP). The main clinical and laboratory parameters during follow-up are reported in the Appendix (item S2).

Treatment was multifactorial and aimed, from commencement of the nephrology follow-up, at optimizing metabolic and hypertension control. Overall, the therapy was maintained throughout follow-up (Table 2), while drug dosing was frequently modified (in 53 % of the 125 visits performed from 1999 to 2015). Adherence to dietary recommendations was adequate, with protein and salt intake consistently ranging 0.6–1.0 g/kg/day and 5–10 g/day, respectively, as testified by the multiple measurements of 24 h urinary excretion of urea and sodium.

Repeated obstructive AKI episodes due to left ureteral stenosis required permanent percutaneous nephrostomy in 2001. These episodes, and complications related to surgery, caused a 10 ml-decrement of eGFR from 17.4 in 1999 to 7.8 ml/min/1.73 m^2 in 2004. In the subsequent decade,

Table 2 Prescribed therapy and dosage in the last 3 months (April to June 2015)

Salt intake	5.0 g/day
Protein intake	0.6 g/kg/day
Ranitidine	150 mg/day
Torasemide	10 mg/day
Sevelamer carbonate	2.4 g/day
Ferrous sulfate	105 mg/day
Sodium bicarbonate	2.0 g/day
Amlodipine	10 mg/day
Methoxy polyethylene glycol-epoietin β	50 μg/month
Ramipril	5.0 mg/day
Atorvastatin	20 mg/day
Paricalcitol	1.0 μg/day
Insulin lispro	4 U + 14 U + 10 U/day
Insulin glargin	16 U/day

eGFR remained remarkably stable, with a total eGFR loss of about 1.0 ml/min. In 2002, the low eGFR levels led us to prepare the patient for hemodialysis as she refused PD and was ineligible for preemptive transplantation; two consecutive native arteriovenous fistulae (AVF) were therefore prepared but both of them failed to mature. On the other hand, the stability of her clinical and metabolic parameters, and the immediate prevention of acute complications such as volume expansion or hyperkalemia, allowed us to safely avoid acute RRT. The patient did not develop an impaired nutritional status and/or inflammation, as evidenced by persistent normality of body mass index (BMI), ferritin, leucocytes count, and albumin.

During the 2004–2012 period, associated with the slight decline of eGFR from 8 to 6 ml/min, proteinuria decreased from 2.5 to 0.6 g/24 h, on average. The reduction of proteinuria was, at least in part, independent of the modest eGFR decline; the two parameters in fact did not correlate ($n = 42$, $r = -0.127$, $p = 0.423$) and the proteinuria/eGFR ratio halved (from 0.22 ± 0.15 to 0.10 ± 0.05 g/ml eGFR). Thereafter, 24-h urine collection was no longer possible, because the patient became blind at the end of 2012 due to the irreversible worsening of diabetic retinopathy.

At the last control (May 2015), the patient was free of asthenia, dyspnea, and peripheral and pulmonary edema; BP was 144/50 mmHg without orthostatism, heart rate 84 b/m, eGFR 5.6 ml/min/1.73 m^2, sK 4.2 mEq/L, HCO_3 24 mEq/l, urea 190 mg/dl. In the previous month, a computed tomography (CT) of the thorax showed a calcified granuloma and multiple calcified lymphadenopathies in the left lung, diffuse interstitial thickening in both lungs without cavity or pleural effusion. Echography showed that the left kidney was small with no dilation of pelvis and correct location of nephrostomy. Vascular calcifications were evident in the main abdominal aortic branches. Echocardiography concomitant to the last visit showed left ventricular hypertrophy (77 g/$h^{2.7}$) with preserved ejection fraction (70.4 %) and a normal inferior cava vein (diameter 1.3 cm, collapsibility index 69.2 %). Diastolic function showed a type II pattern (pseudonormal, E 6 cm/s and E/e′ 21.3).

A few days after the last control visit, the patient developed oliguric AKI because of persistent hyperglycemia, ascribed to repeated errors in insulin dosing, with dependent volume depletion; unfortunately, renal function did not recover after medical therapy and she started chronic RRT, at the age of 68 years, after a period of 15 years spent in CKD stage 5.

Comments

Our systematic review of the literature suggests that the nephrologist intervention allows to safely prolong, for up to 4 years on average, dialysis-free survival in older patients with advanced CKD. Our case report may extend the efficacy of conservative management to both long-term (15 years) and younger (middle-aged) patients.

The striking feature of this case report is the prolonged regular follow-up in Nephrology care (16 years, 125 visits). We therefore had the opportunity to observe the maintenance of eGFR, even if remarkably low, for an extended period of time (about 15 years at CKD-stage 5). To our knowledge, this is the longest stability of "predialysis" renal function ever described. Notably, this remarkable stability was observed in a patient at high risk of ESRD because of her age (she was 52 years old when she started nephrology care with eGFR < 20 ml/min), had long-standing DM1 with microvascular damage (retinopathy leading to blindness), severity of renal disease (single kidney with nephrostomy), and multiple intercurrent AKI episodes.

Histological characterization of renal damage was not obtained because the single functioning kidney contraindicated biopsy. Furthermore, we did not measure true GFR; however, the Modification of Diet in Renal Disease (MDRD)-eGFR shows an adequate performance in advanced CKD [42]. This holds particularly true in the absence of under-nutrition [43], as in the case of this patient. The enduring severity of disease was further supported by the multiple 24-h creatinine clearance measurements obtained, which were similar to eGFR values and consistently below 15 ml/min.

It is reasonable to hypothesize that the intensive nature of the nephrology care may have played a major role in determining the non-progressive status. In this regard, we recently evidenced in a cohort of 729 CKD patients with

advanced disease (79 % in stage 3–4), selected from our outpatient renal clinic on the basis of availability of diagnosis of underlying renal disease, that adequate control of hypertension, anemia and proteinuria in the first year of nephrology care halves the risk of ESRD over the subsequent 5 years [34]. Of note, this association was independent of the nature of primary renal disease, suggesting that the heterogeneous risk of progression, which is intrinsic to each type of underlying disease, may be homogeneously reduced by nephrology care.

In our patient, therapy was not only multifaceted but also frequently modified to optimize control of main risk factors. In the last decade, in fact, a constant control of hypertension, anemia, glycemia and proteinuria was associated with remarkable stability of renal function in our patient. In particular, we observed a decrement of 24-h proteinuria, both as an absolute or eGFR-standardized value. Nowadays, the reduction of proteinuria is recognized as the main predictor of better renal survival [44]. Besides BP and anemia control and anti renin-angiotensin system (anti-RAS) therapy, the long-lasting adherence to prescribed dietary salt and protein restriction, as well as the glycemic control and treatment with active vitamin D possibly contributed to the observed proteinuria reduction [45–48].

We had planned to start RRT at some point of time; two AVFs were in fact prepared though unsuccessfully. However, the adequate control of extracellular volume and metabolic parameters never prompted us to implement emergency dialysis. Therefore, we periodically faced the critical question on the timing of chronic dialysis start in this asymptomatic patient. This question remains a common one in renal clinics today, especially when nephrology follow-up is prolonged, as in the case of our patient.

Conclusions

No evidence-based indication on the correct timing of RRT start is today available. The available literature is in fact limited. Further studies are definitely needed in the Nephrology setting with more appropriate design, longer follow-up and, particularly, in larger patient populations including all age strata. Results of the ongoing European QUALity Study on treatment in advanced chronic kidney disease (EQUAL study) may probably shed some more light on this controversial issue; however, also this study will provide information limited only to patients of 65 years and older [http://www.equal-study.org/it/].

Our systematic analysis and case report suggest that close monitoring and multifactorial care by the nephrologist may allow to maintain ‘pre-dialysis’ renal function over the long term independently of age. While awaiting for new solid evidence, the decision on dialysis start should be personalized, taking into account the global clinical and metabolic picture rather than being dictated only by specific abnormalities or fixed GFR thresholds [2, 4]. Notably, the careful attempts to maintain ESRD patients dialysis-free should be pursued not only for the sake of improving prognosis and quality of life of patients but also because the economic resources today available for health care are limited. Therefore, postponing RRT, even for a few months, may also translate into major savings for the health system dialysis budget [37, 49, 50]. This “saved” money could be wisely used to potentiate renal clinics dedicated to the prevention of ESRD.

Compliance with ethical standards

Conflict of interest The authors have no potential conflict of interest.

Ethical approval This article does not contain any study with human participants or animals performed by any of the authors.

Informed consent Patient gave informed consent to report her clinical case on a scientific journal.

References

1. Bargman JM (2015) Timing of initiation of RRT and modality selection. Clin J Am Soc Nephrol 10(6):1072–1077
2. Davison SN, Levin A, Moss AH et al (2015) Executive summary of the KDIGO controversies conference on supportive care in chronic kidney disease: developing a roadmap to improving quality care. Kidney Int 88(3):447–459
3. van de Luijtgaarden MW, Noordzij M, Tomson C et al (2012) Factors influencing the decision to start renal replacement therapy: results of a survey among European nephrologists. Am J Kidney Dis 60(6):940–948
4. Tattersall J, Dekker F, Heimbürger O et al (2011) ERBP advisory board. When to start dialysis: updated guidance following publication of the initiating dialysis early and late (IDEAL) study. Nephrol Dial Transpl 26(7):2082–2086
5. O’Connor NR, Kumar P (2012) Conservative management of end-stage renal disease without dialysis: a systematic review. J Palliat Med 15(2):228–235
6. Brunori G, Viola BF, Parrinello G et al (2007) DODE study. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. Am J Kidney Dis 49(5):569–580
7. Cooper BA, Branley P, Bulfone L et al (2010) IDEAL study. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 363(7):609–619
8. Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE (2007) Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transpl 22(7):1955–1962
9. Carson RC, Juszczak M, Davenport A, Burns A (2009) Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? Clin J Am Soc Nephrol 4(10):1611–1619

10. Chandna SM, Da Silva-Gane M, Marshall C, Warwicker P, Greenwood RN, Farrington K (2011) Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. Nephrol Dial Transpl 26(5):1608–1614
11. Da Silva-Gane M, Wellsted D, Greenshields H, Norton S, Chandna SM, Farrington K (2012) Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. Clin J Am Soc Nephrol 7(12):2002–2009
12. Seow YY, Cheung YB, Qu LM, Yee AC (2013) Trajectory of quality of life for poor prognosis stage 5D chronic kidney disease with and without dialysis. Am J Nephrol 37(3):231–238
13. Hussain JA, Mooney A, Russon L (2013) Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. Palliat Med 27(9):829–839
14. Shum CK, Tam KF, Chak WL, Chan TC, Mak YF, Chau KF (2014) Outcomes in older adults with stage 5 chronic kidney disease: comparison of peritoneal dialysis and conservative management. J Gerontol A Biol Sci Med Sci 69(3):308–314
15. Crews DC, Scialla JJ, Boulware LE et al (2014) Comparative effectiveness of early versus conventional timing of dialysis initiation in advanced CKD. Am J Kidney Dis 63(5):806–815
16. Shih CJ, Chen YT, Ou SM, Yang WC, Kuo SC, Tarng DC, Taiwan Geriatric Kidney Disease Research (TGKD) Group (2014) The impact of dialysis therapy on older patients with advanced chronic kidney disease: a nationwide population-based study. BMC Med 12:169. doi:10.1186/s12916-014-0169-3
17. Rennke HG, Anderson S, Brenner BM (1989) Structural and functional correlations in the progression of renal disease. In: Tisher CC, Brenner BM (eds) Renal pathology. Lippincott, Philadelphia, p 43
18. Brenner BM (2003) Retarding the progression of renal disease. Kidney Int 64(1):370–378
19. Maschio G, Oldrizzi L, Rugiu C (1991) Is there a "point of no return" in progressive renal disease? J Am Soc Nephrol 2(4):832–840
20. Rosansky SJ (2012) Renal function trajectory is more important than chronic kidney disease stage for managing patients with chronic kidney disease. Am J Nephrol 36(1):1–10
21. Eriksen BO, Ingebretsen OC (2006) The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int 69(2):375–382
22. O'Hare AM, Choi AI, Bertenthal D et al (2007) Age affects outcomes in chronic kidney disease. J Am Soc Nephrol 18(10):2758–2765
23. Al-Aly Z, Zeringue A, Fu J, Rauchman MI et al (2010) Rate of kidney function decline associates with mortality. J Am Soc Nephrol 21(11):1961–1969
24. Perkins RM, Bucaloiu ID, Kirchner HL et al (2011) GFR decline and mortality risk among patients with chronic kidney disease. Clin J Am Soc Nephrol 6(8):1879–1886
25. Li L, Astor BC, Lewis J et al (2012) Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis 59(4):504–512
26. De Nicola L, Minutolo R, Chiodini P et al (2012) The effect of increasing age on the prognosis of non-dialysis patients with chronic kidney disease receiving stable nephrology care. Kidney Int 82(4):482–488
27. Hunsicker LG, Adler S, Caggiula A et al (1997) Predictors of the progression of renal disease in the modification of diet in renal disease study. Kidney Int 51(6):1908–1919
28. Levin A, Djurdjie O, Beaulieu M, Er L (2008) Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis 52(4):661–671
29. Conway B, Webster A, Ramsay G et al (2009) Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease. Nephrol Dial Transplant 24(6):1930–1937
30. Weis L, Metzger M, Haymann JP, Nephro Test Study Group et al (2013) Renal function can improve at any stage of chronic kidney disease. PLoS One 8(12):e81835
31. Jones C, Roderick P, Harris S, Rogerson M (2006) Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. Nephrol Dial Transpl 21(8):2133–2143
32. Tseng CL, Kern EF, Miller DR et al (2008) Survival benefit of nephrologic care in patients with diabetes mellitus and chronic kidney disease. Arch Intern Med 168(1):55–62
33. Smart NA, Titus TT (2011) Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. Am J Med 124(11):1073–1080
34. De Nicola L, Provenzano M, Chiodini P et al (2015) Independent role of underlying kidney disease on renal prognosis of patients with chronic kidney disease under nephrology care. PLoS One 10(5):e0127071
35. Wong CF, McCarthy M, Howse ML, Williams PS (2007) Factors affecting survival in advanced chronic kidney disease patients who choose not to receive dialysis. Ren Fail 29(6):653–659
36. De Biase V, Tobaldini O, Boaretti C et al (2008) Prolonged conservative treatment for frail elderly patients with end-stage renal disease: the Verona experience. Nephrol Dial Transpl 23(4):1313–1317
37. Di Micco L, Torraca S, Pota A et al (2009) Setting dialysis start at 6.0 ml/min/1.73 m2 eGFR—a study on safety, quality of life and economic impact. Nephrol Dial Transpl 24(11):3434–3440
38. Ellam T, El-Kossi M, Prasanth KC, El-Nahas M, Khwaja A (2009) Conservatively managed patients with stage 5 chronic kidney disease—outcomes from a single center experience. QJM 102(8):547–554
39. Dattolo P, Michelassi S, Amidone M (2015) Structured clinical follow-up for CKD stage 5 may safely postpone dialysis. J Nephrol 28(4):463–469
40. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE (2009) Functional status of elderly adults before and after initiation of dialysis. N Engl J Med 361(16):1539–1547
41. Conte G, Iavarone M, Santorelli V, De Nicola L (1997) Acute renal failure of unknown origin. Don't forget renal tuberculosis. Nephrol Dial Transpl 12(6):1260–1261
42. Evans M, van Stralen KJ, Schön S, ERA-EDTA Registry, Swedish Renal Registry Collaboration et al (2013) Glomerular filtration rate-estimating equations for patients with advanced chronic kidney disease. Nephrol Dial Transpl 28(10):2518–2526
43. Grootendorst DC, Michels WM, Richardson JD, NECOSAD Study Group et al (2011) The MDRD formula does not reflect GFR in ESRD patients. Nephrol Dial Transpl 26(6):1932–1937
44. Lambers Heerspink HJ, Kröpelin TF, Hoekman J, de Zeeuw D, on behalf of the Reducing Albuminuria as Surrogate Endpoint (REASSURE) Consortium (2015) Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. J Am Soc Nephrol 26(8):2055–2064
45. Hansen HP, Christensen PK, Tauber-Lassen E, Klausen A, Jensen BR, Parving HH (1999) Low-protein diet and kidney function in insulin-dependent diabetic patients with diabetic nephropathy. Kidney Int 55(2):621–628
46. Lambers Heerspink HJ, Holtkamp FA, Parving HH et al (2012) Moderation of dietary sodium potentiates the renal and

cardiovascular protective effects of angiotensin receptor blockers. Kidney Int 82(3):330–337
47. De Nicola L, Conte G, Russo D, Gorini A, Minutolo R (2012) Antiproteinuric effect of add-on paricalcitol in CKD patients under maximal tolerated inhibition of renin-angiotensin system: a prospective observational study. BMC Nephrol 13:150. doi:10.1186/1471-2369-13-150
48. de Boer IH, Afkarian M, Rue TC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group et al (2014) Renal outcomes in patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol 25(10):2342–2350
49. Scalone L, Borghetti F, Brunori G et al (2010) Cost-benefit analysis of supplemented very low-protein diet versus dialysis in elderly CKD5 patients. Nephrol Dial Transpl 25(3):907–913
50. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B (2012) Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transpl 27(S3):73–80