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With blog commentary

Vegetarian low-protein diets supplemented with keto analogues: a niche for the few or an option for many?

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ORIGINAL ARTICLE

ABSTRACT

Background. Low-protein diets are often mentioned but seldom used to slow chronic kidney disease (CKD) progression. The aim of the study was to investigate the potential for implementation of a simplified low-protein diet supplemented with alpha-keto analogues (LPD-KA) as part of the routine work-up in CKD patients.

Methods. In an implementation study (December 2007–November 2011), all patients with CKD Stages IV–V not on dialysis, rapidly progressive Stage III and/or refractory proteinuria, were offered either a simplified LPD-KA, or commercially available low-protein food. LPD-KA consisted of proteins 0.6 g/kg/day, supplementation with Ketosteril 1 pill/10 Kg, 1–3 free-choice meals/week and a simplified schema based on 'allowed' and 'forbidden' foods. 'Success' was defined as at least 6 months on LPD-KA. Progression was defined as reduction in glomerular filtration rate (GFR)[(Chronic Kidney Disease Epidemiology Collaboration) formula CKD-EPI] in patients with at least 6 months of follow-up.

Results. Of about 2500 patients referred (8% CKD Stages IV–V), 139 started LPD-KA; median age (70 years) and prevalence of comorbidity (79%) were in line with the dialysis population. Start of dialysis was the main reason for discontinuation (40 cases, unplanned in 7); clinical reasons were recorded in 7, personal preference in 14 and improvement and death in 8 each. The low gross mortality (4% per year) and the progression rate (from −8 to 0 mL/min/year at 6 months) are reassuring concerning safety. None of the baseline conditions, including age, educational level, comorbidity or kidney function, discriminated the patients who followed the diet for at least 6 months.

Conclusions. Our data suggest a wider offer of LPD-KA to patients with severe and progressive CKD. The promising results in terms of mortality and progression need confirmation with different study designs.

INTRODUCTION

Chronic kidney disease (CKD) is a major health care problem, and retarding its evolution to end-stage renal disease (ESRD) has obvious clinical and economic implications [1, 2]. The first attempts to modulate kidney function via the diet date back to over a century ago, and the systematic studies of

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Thomas Addis, on which low-protein diets are still extensively based, were published over 60 years ago [3–5]. In spite of several trials conducted during the last decade, the role of low-protein diets remains controversial with discrepancies between results in intention-to-treat analysis and those in per-protocol analysis [6–14]. However, it is now usually held that the effect of a low-protein diet on the progression of CKD becomes evident only when protein intake is <0.8 g of proteins/kg/day. Milder regimens may have an effect as 'metabolic stabilizers', a new concept that underlines the clinical and economical advantages of even relatively small 'gains' in a pre-dialysis phase [15].

A regimen with 0.6 g/kg/day of proteins is often difficult, unless either a vegan diet (usually supplemented with essential amino acids and keto acids) is proposed or 'non-proteic' (commercially available) carbohydrates are employed; the combination of both approaches allows protein intakes as low as 0.3 g/kg/day [16–20]. In spite of these problems, a few fundamental systematic reviews have concluded that the experience with low-protein diets is generally positive, at least in selected settings [21, 22].

However, low-protein diets are still under-employed and the main concerns regard their safety and implementation in clinical practice. The comment appearing in The Lancet almost 30 years ago still holds true: 'The practical implications of these ideas are enormous, but the time is not yet ripe for generalized, uncontrolled, application of restricted and unpleasant diets to patients with renal disease' [23]. Indeed, several barriers hinder the application of low-protein diets in CKD patients: they are often 'unpleasant and restricted', impairing long-term compliance; they are difficult to study and they are rather expensive if they employ 'non-proteic' commercial food or keto-acid supplementation [11, 24–27].

Nevertheless, at least three main reasons suggest that the time is 'ripe' for a systematic integration of diet in the clinical treatment of CKD: the cost of dialysis, the clinical advantages and the failure of early dialysis to prolong survival. The global world crisis is challenging all health care systems, and the high costs of dialysis are central to cost containment [1–2, 28]. Recent studies suggest that the 'early dialysis' approaches do not add to survival, thus underlining the advantages of low-protein diets not only in slowing the progression of renal failure, but also as metabolic stabilizers, allowing prolongation of the 'pre-dialysis phase' and ensuring equivalent survival at lower costs [15, 29–31].

Therefore, the present study was designed to investigate the potential for implementation of a simplified approach to a low-protein diet supplemented with alpha-keto analogues (LPD-KA), with a protein intake of 0.6 g/kg/day, as part of the routine clinical work-up in non-selected populations of CKD patients. The study was aimed at answering the question whether it was possible to identify a profile of 'ideal patients' to be prescribed an LPD-KA diet, in keeping with the suggestions in the literature (young, educated and compliant); the absence of a specific profile would suggest offering a diet trial to all CKD patients willing to try it.

MATERIALS AND METHODS

Study setting and 'model of care'

The study was performed in the Outpatient Unit of the Nephrology Unit of San Luigi Hospital, University of Torino, Italy. The unit started its activity on 1 December 2007. Since then, about 2500 patients had been evaluated up to 31 March 2012, and about half had been included into our long-term follow-up. CKD Stages IV–V accounted for about 8% of the cases. In the study setting, a low-protein diet is proposed by the nephrologist to patients with CKD Stages IV–V not on dialysis, with rapid progression of CKD Stage III and/or with refractory nephrotic syndrome.

Three main therapeutic options are discussed: no diet (while the policy of our unit strongly supports the use of low-protein diets, the patient's choice not to change his/her dietary habits is also discussed); low-protein diets at 0.6 g/kg/day of proteins (usually substituting bread, rice and pasta with commercial protein-free carbohydrates); a simplified vegetarian low-protein diet (0.6 g/kg/day) supplemented with alpha-keto analogues (LPD-KA). Further options (vegetarian supplemented diets with very low-protein content: 0.3 g/kg/day, consisting of the simplified LPD-KA plus the substitution of bread, rice and pasta with commercial protein-free carbohydrates; vegan diet without supplementation, rich in legumes, according to Barsotti and co-workers) or moderate reduction of protein intake (0.8 g/kg/day) are discussed in selected cases.

The simplified LPD-KA, on which the present study is focussed, derived from the original scheme of Barsotti and Giovannetti [32, 33], is based on a concept of forbidden and allowed foods (forbidden, except in the context of the free-choice meal(s): fish, meat, milk, eggs and derivates; everything else is allowed). The diet is vegan, with an average of 0.6 g/kg/day protein intake; it is supplemented (Ketosteril 1 cp per 10 kg of body weight, approximated in excess); real weight is considered for prescription, except in cases with high body mass index (BMI), where a compromise between real and ideal weight is individually sought. To improve compliance, 1–3 free-choice meals per week are allowed. The daily energy intake is aimed at 30–35 kcal/kg/day, but as a rule the foods are not weighed and the caloric intake is calculated based on a diet journal after 1–3 weeks. Consultations by the dietician are given on demand.

Study design and population

This is an observational cohort study. All patients who started at least a 1-month trial of LPD-KA between 1 December 2007 and 30 November 2011 were included. The physician extensively discusses the diet; if the patient agrees to test the LPD-KA diet, 1-month KA supplements are given and the patient is scheduled for blood tests and clinical visits within 1 month. All the patients considered in the present analysis returned at the 1-month scheduled visit and reported on their choice to further follow the diet or not; three patients only did not return for the scheduled visit and were excluded from the present analysis.

The follow-up of patients was scheduled as follows: biochemical controls and routine visits are scheduled one per month; further controls are added in selected cases, up to once weekly in 'pre-dialysis' CKD; follow-up is interrupted at the start of dialysis. At each visit, patients undergo physical examination, with particular attention to oedema, and blood pressure as well as weight measurement.

Data collection

Demographic and clinical data were prospectively gathered from the start of the diet until its end, and periodically entered into an electronic database.

Data collected at the start of diet were age, sex, weight, height, BMI, educational level, comorbidities cause of CKD, reasons for choice of the diet and previous low-protein diets. Data collected during the follow-up were cause of death, start of dialysis and circumstances of initiation (planned or not), type of dialysis, reasons for dropping out, side effects of diet and diet compliance.

Compliance is assessed by dietary inquiry and, in stable patients, by Mitch formula on 24-h urine collection, performed avoiding free meals for the previous 2 days [34]. Furthermore, as the patients receive the keto acids at the clinical visits, it is possible to calculate the amount of supplements taken in the period.

We defined dialysis as planned when the start of renal replacement therapy was decided timely enough to allow the positioning of a vascular access (fistula in most of the cases) or a peritoneal access, without need for hospitalization or acute interventions. In the absence of a sharp GFR cut-point for dialysis start, we took into consideration three major items: water–salt overload, with oedema and/or severe hypertension; acid–base imbalance, not corrected by oral bicarbonate; calcium–phosphate and parathyroid hormon imbalance, once more not corrected by oral therapy. Ancillary data were refractory anaemia, or other signs or symptoms of uraemia, such as restless leg syndrome, loss of appetite, weight loss and severe asthenia. Even if a specific cut-point was not defined, controls were intensified <6–7 mL/min of GFR, as a rule from monthly to twice monthly: treatment of the above-mentioned derangements, common in late CKD stages, is obtained by the usual means of good clinical practice. The senior nephrologist of the unit took the final decision on dialysis start.

Biochemical parameters were also collected in the present study and gathered in the database at start and every 6 months: serum creatinine, urea, creatinine clearance, proteinuria and serum albumin. In addition, the following data were gathered for the subset of patients with at least 6 months of follow-up: serum bicarbonate, base excess, urinary urea (24-h urine collection) and bicarbonate supplementation. These parameters were assessed in the laboratory of choice of the patients; about 70% of the patients performed blood and urinary tests in the general laboratory of the hospital. GFR was calculated by Cockcroft and Gault, simplified modification of diet in renal disease formula and CKD-EPI formulae; the latter was chosen for GFR calculation in the present analysis, according to a growing use of this formula, in particular in the elderly population [35].

Statistical analysis

A descriptive analysis was performed as appropriate (median and range in the case of non-parametric data, mean and standard deviation in the case of parametric distribution). Analysis of variance, Kruskal–Wallis, Mann–Whitney, χ^2 and t-test were performed according to standard indications. Descriptive statistics were done overall, by sex, duration of follow-up and according to the causes of drop-out.

Mortality rates were calculated as deaths recorded for 100 patient-years of observation.

The 'gross' progression rate and dietary compliance were assessed in a selected subset of cases, allowing contextualization of the results; the analysis included the patients with baseline GFR <60 and >10 mL/min (thus excluding the patients in which the diet was prescribed for nephrotic syndrome alone), at least 6 months of follow-up on LPD-KA (the time interval usually chosen in 'medium-term' analysis of LPD-KA), who started the diet in our unit and who had pre- and post-LPD-KA renal functional data available, performed in our laboratory.

Logistic regression analysis was performed, considering at least 6 months (and 1 year) of follow-up on the diet as 'outcome'. The data chosen for dichotomization were the nearest rounded numbers to the median in our population.

For this analysis, patients who discontinued because of improved kidney function or death were excluded, as were those in which prescription was done for proteinuria alone (GFR range at start: 10–60 mL/min).

The 'forced entry' method was chosen, due to its simplicity and to the fact that the stepwise methods fit better when several covariates prove to be significant at the univariate analysis.

The covariates entered to in the model were chosen either because of their statistical significance in the univariate analysis [GFR (or creatinine) and proteinuria] or because of their acknowledged relevance for compliance (educational level), CKD progression (diabetes, all comorbidities or proteinuria) and mortality (age, comorbidities and sex), as start of dialysis and mortality 'competes' with a longer duration of the diet.

The following discrete variables were analysed in different combinations: sex, comorbidity (none and one or more) or diabetes (present–absent), and educational level (up to eighth grade, ninth grade and over); the following continuous variables were analysed: age (dichotomized at 70 years), baseline creatinine (dichotomized at 3.5 mg/dL) or, alternatively, baseline GFR (dichotomized at 15 mL/min), baseline proteinuria (dichotomized at 1 g/day).

The analysis was performed with SPSS (version 18.0). The results are expressed as odds ratio (OR). The level of statistical significance was set at <0.5.

RESULTS

Baseline data

The flow chart of the patients who performed at least a 1-month trial of vegetarian LPD-KA is reported in Figure 1 130 patients started the diet in the unit; in addition, nine

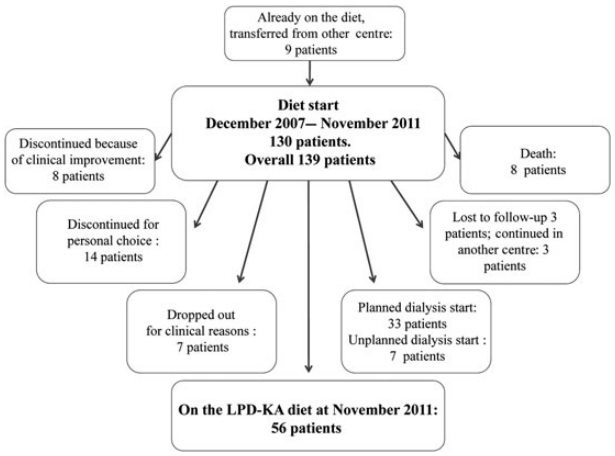

FIGURE 1: Flow chart of patients who started vegetarian LPD-KA.

patients previously followed in a different centre resumed follow-up in our unit; they were all considered in the baseline analysis. The enrolment rate was relatively homogeneous since the start of the activity: 31 cases in the first year of study, 36, 36 and 27 in the following years. In another 15 cases, the diet was prescribed in pregnancy in a dedicated outpatient unit; three patients continued follow-up in our unit after delivery and only they were included in the present analysis, two in the nine patients transferred from another centre and one as new patient. At the time of the study (at the end of the fourth year of activity), 56 patients were on the simplified LPD-KA: 54 on 0.6 g/kg/day protein intake and 2 on a 'very low-protein' supplemented diet (0.3 g/kg/day).

All the clinical parameters were widely scattered, according to the heterogeneity of the population and to the broad clinical indications to the diet (Table 1).

The diet was started or continued in 91 patients with CKD Stages IV–V (91 started and 9 continued), and started in 29 cases with progressive Stage III CKD and in 10 cases for refractory proteinuria (CKD Stages I–II).

This is a relatively old population (median age 70), in line with the median age of 67 of new patients starting dialysis in our region; as in the European ESRD population, nephrosclerosis is the main cause of CKD. Cardiovascular diseases and diabetes are highly prevalent and represent the main comorbid conditions, once more in keeping with the usual features of the CKD population (Table 1). No significant difference in demographic data was found sorting patients according to the duration of follow-up (Table 1).

Reasons for discontinuation and side effects of the diet

The main reason for discontinuation of the diet was the start of dialysis (Table 2). This was planned in 33 (40%) patients and unplanned in 7 (8%). An unplanned dialysis start was needed because of an acute cardiovascular accident (myocardial infarction in three cases), an acute infectious problem (sepsis in three cases), and kidney rupture and massive bleeding in one patient with polycystic kidney disease. Dialysis was not started in emergency for acute pulmonary oedema or hyperkalaemia linked to uncontrolled worsening of CKD in any patient (Figure 1 and Table 2). Eight patients died (five of cardiovascular accidents, two of neoplasia and one of sepsis).

Overall gross mortality on the diet was 4.4 cases per 100 patient-years of observation (eight cases over 181 patient-years on the diet), compared with over 10% in the first year of dialysis in our area. These mortality data are confirmed also including in the evaluation the first year of follow up of patients who dropped-out the diet (included the ones who started dialysis).

Clinical reasons, none of which were severe (gastrointestinal intolerance and/or peripheral oedema), were the cause of discontinuation in seven (8%) patients. Fourteen (16%) patients discontinued the diet by their own choice: the reason was mainly the monotony of the diet and the need for 'too many pills' in addition to the complex polypharmacy. Three of them shifted from LPD-KA to standard LPDs with commercial products. Seven patients dropped out in the first 3 months and only one after a long follow-up (97 months). Only three (4%) patients were lost to follow-up and 3 (4%) continued their follow-up in another centre.

In eight (10%) patients, the clinical conditions improved enough to allow discontinuation of the diet. In five cases, clinical improvement was due to optimization of the therapy (focal segmental glomerulosclerosis starting cyclosporine A, IgA nephropathy treated with prednisone and angiotensin converting enzyme inhibitors, retroperitoneal fibrosis, obstructive nephropathy and pulmonary neoplasia starting chemotherapy), while in the remaining three cases the clinical conditions stabilized after 7–8 months of diet, allowing resumption of a free-choice dietary regimen (Table 2).

Eighteen patients were counselled by a dietician; the main reasons were: improvement of compliance, or patient's request: seven cases; need for weight loss: four cases; underweight: three cases; presence of other relevant clinical problems potentially interfering with the diet: three cases (active collagen disease, Chron's disease and liver disease) and need for adaptation of Ayurveda diet: one case.

Progression of kidney disease

In the subset of cases analysed, the median GFR decrease was −4 mL/min/6 months (corresponding to −8 mL/min/year) before starting the diet, and kidney function decreased less steeply and stabilized in the cases who 'remained on the diet'; the wide range of kidney functional data has to be underlined (Figure 2 and Table 3). The median progression (loss of GFR) was not modified in the patients who dropped out in the first 6 months (median GFR decrease: −10 mL/min/year), and the value decreased to −6 mL/min/year in the patients who dropped out after 6–12 months. Albumin and total protein levels remained stable throughout the study period (Table 3).

The median HCO_3 at 6 months was 26.5 mmol/L (range 18.8–34.4 mmol/L), with base excess 1.45 (range −7/+12); 20 patients were not on oral bicarbonates at start and did not need them after 6 months of diet; 20 continued the supplementation, 6 started it, 1 reduced the doses and 1 discontinued it.

In the same selected subset of stable patients, according to the Mitch formula, at 6 months, median protein intake was 0.5 g/kg/day (range 0.34–0.71 g/kg/day).

Table 1. Baseline data: all patients with at least a 1-month trial are considered

	All patients (139)	Males (93)	Females (46)	P-value	Follow-up ≤1 month (22)	Follow-up 2–5 months (22)	Follow-up ≥6 months (95)	P-value
Males/females	66.9%	–	–	–	63.6%	72.7%	66.3%	ns
Age median (range)	70 (27–91)	70 (27–91)	69.5 (30–88)	ns	69.5 (30–84)	72 (53–85)	69 (27–91)	ns
Educational level (>eighth degree)	51.9%	62.4%	23.9%	<0.001	47.1%	68.2%	48.9%	ns
BMI median (range)	26.1 (16.3–44.9)	26.1 (16.3–35.9)	27.3 (16.8–44.9)	ns	26.7 (16.8–44.9)	25.8 (19.5–35.9)	26.1 (16.3–43.0)	ns
Renal disease								
Glomerulonephritis (%)	19.4	23.7	10.9	0.02	18.2	13.6	21.1	ns
Diabetic nephropathy (%)	17.3	12.9	26.1	0.02	9.1	4.5	22.1	ns
Nephrosclerosis (%)	35.3	37.6	30.4	ns	45.5	50	29.5	ns
Serum creatinine at start median (range)	3.2 (0.8–16)	3.4 (0.8–16)	3.0 (1.3–10)	ns	3.12 (1.7–16)	3.77 (1.88–6.67)	3.0 (0.87–6.7)	0.05
GFR at start (CKD-EPI) median (range)	17 (3–110)	17 (3–110)	16 (5–48)	ns	17 (3–44)	13.5 (7–37)	17.5 (8–110)	0.05
Proteinuria 24 h at start median (range)	1.4 (0–18)	1.75 (0–18)	0.9 (0–8.9)	0.045	1.25 (0–17.8)	1.6 (0–18)	1.4 (0–10.4)	ns
Diabetes (%)	40.3	38.7	43.5	ns	27.3	36.4	44.2	ns
Cardiovascular comorbidity (%)	41.7	47.3	30.4	ns	45.5	54.5	37.9	ns
Neoplasia (%)	19.4	25.8	6.5	0.013	9.1	31.8	18.9	ns
No comorbidity (%)	20.9	16.1	30.4	ns	18.2	13.6	23.2	ns
≥2 comorbid factors (%)	45.3	47.3	41.3	ns	36.4	63.6	43.2	ns

P-values were calculated by: χ^2 test, Kruskal–Wallis test and Mann–Whitney *U*-test.
A renal biopsy was performed in 11 diabetic patients (two with diabetic nephropathy and nine with other kidney diseases); and in the other cases, diabetic nephropathy was defined by a 'classic clinical course' with intense proteinuria, consensual target organ lesions and no evidence of other renal diseases.

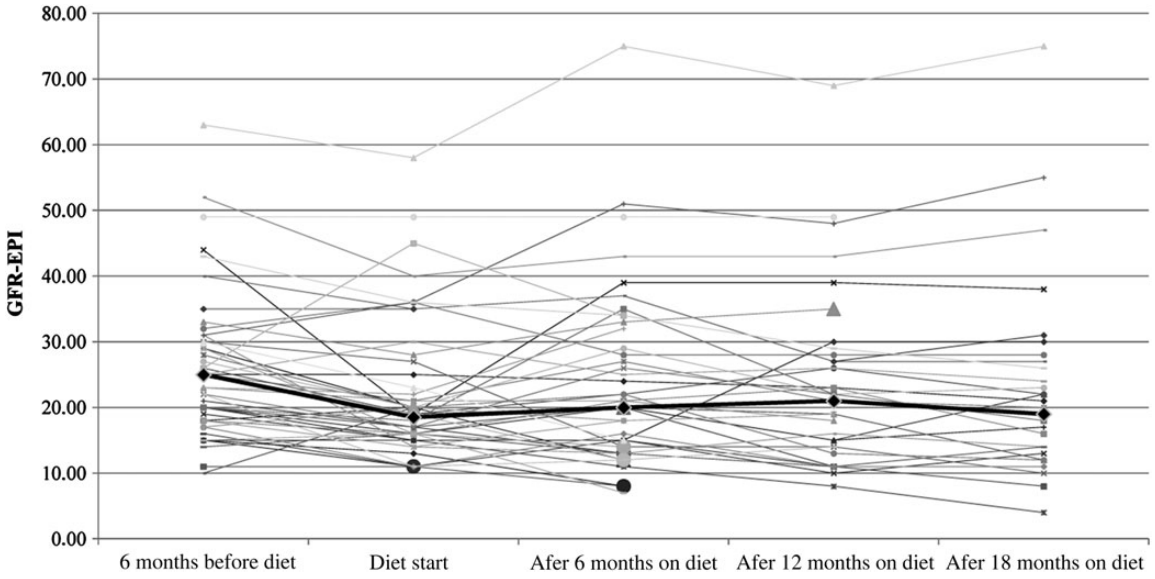

FIGURE 2: Graphical representation of the value of GFR-EPI for each patient. Filled triangle: last update before death; filled circle: last update before dialysis start; filled square: median GFR-EPI and trend.

Prediction of follow-up of at least 6 months on the diet

Table 4 reports the results of the multivariate analysis, considering 'success' as a duration of the diet of at least 6 months. None of the tested parameters, including age, sex, educational level and comorbidity, was predictive of 'success' of the diet, thus failing to identify the elements for an *a priori* definition of a profile of CKD patients in which a LPD-KA is likely to be followed for a relatively long time. The results were confirmed when serum creatinine (dichotomized at 3.5 mg/dL) was considered instead of GFR and also, in the smaller subset of cases who started the diet before November 2010, when the prescription 'success' was set at 1 year.

DISCUSSION

The present implementation study was aimed at testing our simplified approach to a LPD-KA (protein intake of 0.6 g/kg/day) in patients with severe or progressive CKD referred to a new nephrology unit. Flexibility starts from prescription, as the diet is simply based on allowed and forbidden foods, without the need to weigh all foods; 1–3 free-choice meals are allowed to reduce the psychological burden and to avoid malnutrition. The diet is initially proposed as a 1-month trial and is prescribed and controlled by the nephrologist in the context of the routine clinical follow-up. This schema was developed, following a few pilot experiences in smaller subsets of patients, on the hypothesis that a simplified approach using a 'not-too-strict' diet (0.6 g/kg/day of proteins) was feasible and could provide positive results with a low risk of side effects [36, 37].

The subset of cases who started the LPD-KA diet was in line with the population starting dialysis in our region in terms of age (median 70 years) and high prevalence of diabetes, nephrosclerosis and multiple comorbidities (Table 1). The enrolment rate on the diet was relatively high; about 5% of all patients followed in our unit experienced at least one trial of LPD-KA and the figure rose to over 30% of the referred patients with CKD Stages IV and V.

An interesting suggestion of our study, needing confirmation on a larger scale, with higher statistical power, is the lack of strong clinical and demographic elements for an *a priori* definition of 'good' candidates for LPD-KA, considering 'prescription success' as at least 6 months of follow-up (Table 4). It is noteworthy that educational level (often associated with higher compliance), diabetes, overall comorbidity (often associated with poor dietary compliance) and old age (frequently considered to impair efficient modulation of the diet) are not confirmed as strong relevant factors in attaining the medium-term follow-up of the diet, at least in this relatively small population.

Interestingly, at least in stable patients with at least 6 months of follow-up, compliance was impressive, with a median protein intake of 0.5 g/kg/day, calculated at distance from the free meals. This supports the hypothesis that subtle personal preferences, as well as clear motivations, are fundamental in the relationship with food and diet. Therefore, the diet should be proposed to all patients without preclusion (Table 4).

In view of the main finding, our study prompts several further observations worth discussing. Possibly because of the flexible policy, the allowance of free-choice meals and the strict control policy, there were few clinical reasons for discontinuation, and no case of malnutrition was recorded as a cause of discontinuation. Conversely, psychological reasons for dropping out were more common, underlining the strong negative effect of monotony of the dietary regimen and the need for several 'pills', usually in the context of a complex polypharmacy (Table 2). The start of dialysis was the main cause of discontinuation of the diet (Table 2). In this series, all the patients who needed unplanned dialysis experienced acute clinical problems, related more to the clinical conditions than to the diet and the advanced CKD; this subset of patients

Table 2. Reasons of discontinuation: all patients

	Death (8)	Planned dialysis start (33)	Un-planned dialysis start (7)	Patient's choice (14)	Clinical reasons (7)	Improved (8)	Lost to follow-up—transferred to another centre (6)	On the diet at 30 November 2011 (56)	P-value
Age median (range)	74.5 (57–86)	66 (30–85)	70 (35–76)	64 (43–79)	74 (59–81)	75.5 (49–88)	72.5 (31–84)	69.5 (27–91)	0.39
Educational level >eighth degree (%)	25	60.6	42.9	71.4	28.6	25	50	54	0.21
Serum creatinine at start median (range)	3.2 (2.08–5)	4.6 (2.9–16)	3.5 (1.7–6.2)	2.5 (1.2–5.5)	2.2 (1.8–5.1)	2.8 (1.7–5.0)	3.4 (2.9–3.9)	2.8 (0.8–6.7)	<0.001
GFR at start (CKD-EPI) median (range)	16 (8–28)	11 (3–20)	11 (8–41)	23 (10–67)	27 (9–31)	17 (12–40)	19 (11–25)	20 (8–110)	<0.001
Proteinuria 24 h median (range)	0.2 (0–1.5)	2.15 (0.2–18)	1.5 (0.8–4.6)	1.6 (0–10.4)	0.7 (0.3–4.7)	0.5 (0.1–4.5)	2.75 (0.7–4.9)	1.4 (0.1–8.2)	0.01
No comorbidity (%)	0	21.2	14.3	14.3	14.3	25	50	23.2	0.51
≥2 comorbid factors (%)	87.5	36.4	71.4	35.7	71.4	37.5	33.3	42.9	0.10

P-values were calculated by: χ^2 test and Kruskal–Wallis test.

Table 3. Main data at the intervals considered and main GFR loss, in patents with at least 6 months of follow-up and data available in our laboratory

	−6 months (49 cases)	Start (82 cases)	+6 months (60 cases)	+12 months (46 cases)	+18 months (38 cases)
All cases with at least 6 months of follow-up (data from the same laboratory)					
GFR-EPI (mL/min)	25 (10–63)	18.50 (10–58)	20 (7–75)	21 (6–69)	19 (4–75)
Total proteins (g/dL)	7.20 (5.3–8.5)	6.90 (4.1–8.6)	7.20 (4.6–8.4)	6.80 (5.1–8.9)	6.90 (5.3–7.9)
Albumin (g/dL)	3.71 (1.9–4.5)	3.80 (1.4–4.8)	4.00 (1.8–4.9)	4.14 (2.8–5.4)	3.70 (2.4–4.7)
		−6 months to start (48 cases)	0–6 months (48 cases)	6–12 months (34 cases)	12–18 months (28 cases)
Only patients with at least 6 months of follow-up, who started in the unit, with available data in our laboratory before and after the start of the diet					
Loss of GFR (mL/min/6 months):		−4 (−25 to +19)	0 (−13 to +20)	−3 (−13 to +15)	−1 (−7 to +7)
GFR-EPI at the interval (mL/min)	25 (10–63)	19.50 (11–58)	20 (7–75)	22 (8–69)	20.50 (4–75)

Table 4. Logistic regression analysis, considering a follow-up on the diet of at least 6 months as outcome

N = 100	Number in group	Follow-up ≥6 months	OR	95% CI
Age <70	47	37		
Age ≥70	53	38	0.71	0.22–2.29
Females	34	26		
Males	66	49	1.57	0.44–5.55
Educational level up to the eighth grade	46	36		
Educational level above the eighth grade	53	38	0.41	0.12–1.43
Diabetes (absence)	60	43		
Diabetes (presence)	40	32	1.59	0.55–4.64
No comorbidity	21	18		
Presence of at least one comorbidity	79	57	0.13	0.01–1.27
GFR-EPI <15 mL/min	40	27		
GFR-EPI ≥15 mL/min	59	48	1.99	0.69–5.66
Proteinuria <1 g/day	34	25		
Proteinuria ≥1 g/day	60	48	1.44	0.49–4.23

For this analysis, patients who discontinued because of improved kidney function or death were excluded, as were those in which prescription was done for proteinuria alone (GFR range at start: 10–60 mL/min).

shared higher age and prevalence of comorbidities with the patients who died while continuing the diet (Table 2).

The low mortality rates (4.4 cases per 100 patient-year), within the limits of relatively small numbers and short follow-up, give further reassurance that there is no negative impact of LPD-KA in our population; our data are in the same line of other reports of long-term safety of LPD-KA, as the important long-term analysis of the French school, regarding patients treated by very low-LPD-KA, observed after the start of dialysis [17].

Our study was neither designed nor sufficiently powerful to demonstrate an effect on the progression of CKD. Routine laboratory data, such as creatinine clearance, lack the precision of isotopic or inulin clearances. Within these limits, the analysis of the progression rate (performed to allow contextualization of our results), suggest that at least patients with longer follow-up may stabilize on the LPD-KA diet, an issue to be confirmed on larger numbers and longer follow-up (Table 3).

In this regard, even a small delay of dialysis is potentially highly favourable in terms of costs. In our area, 1 year of dialysis corresponds to 35–60 patient-years on LPD-KA, based on the regional data indicating the costs of dialysis to be 35–60 000 Euros per year and assuming that the costs of the LPD-KA correspond to the supplements, averaging 1000 Euros per year (0.4 Euros per pill, 8 pills per day, 330 days per year) [38].

This analysis has some strong points: it demonstrates that LPD-KA is feasible outside of the few large referral centres where much of the experimental data have been collected, at least in a relevant percentage of patients with severe CKD. The low drop-out rate (not considering clinical improvement, death and start of dialysis, as the diet is aimed at prolonging dialysis-free survival) is in keeping with this observation. It underlines the importance of the 'patient effect' in the choice of the diet, thus arguing against the often-held conception that LPD-KA is too difficult 'for the patients'. It also demonstrates that a relatively 'soft and flexible' LPD-KA (0.6 g/kg/day, with 1–3 free-choice meals per week) may become part of the clinical nephrology routine, in keeping with a long-lasting experience of diet management by nephrologists [3, 9, 15, 19, 28, 32, 33].

Last but not least, it adds some mortality data, suggesting that the low mortality rates (4.4 per 100 patient-years) may be taken as an indication of the safety of LPD-KA.

Our study also has several shortcomings, partly shared with similar study designs. Implementation studies are not randomized and thus are more apt to define practical strategies than to assess treatment efficacy [39, 40]. This suggests that our favourable data on progression and mortality should be considered only indicative and as a stimulus for further analysis. Even more importantly, a control group of patients who choose either no diet or a different LPD (for example with commercial food) was not available for the present analysis; such an analysis is planned in the context of a perspective study, including all CKD Stage IV–V patients followed in our unit. The number of cases is still limited, in particular after the selections needed for statistical analyses. However, this limit is shared by several studies dealing with clinical practice, in which the quality of data may differ from randomized trials; indeed, in the last decade, a few series report on over 100 patients on LPD-KA, with a range from a few cases in short-term metabolic assessments (16 on LPD-KA a recent

randomized controlled trial by Di Iorio) to 203 in the large French study on the outcome of dialysis of patients previously treated by very low-LPD-KA for at least 3 months [22, 36, 41].

Within these limits, our data support a wider use of LPD-KA as an option to be offered to all patients with advanced or progressive CKD. Further studies are needed to assess the clinical (in particular as for mortality rates) and economic advantages of LPD-KA, also taking into account the support therapies and the indications for dialysis, and to confirm the feasibility of our simplified dietary programme in different clinical settings.

CONCLUSIONS

The data obtained in this feasibility study may support a wider offer of LPD-KA to patients with severe and progressive CKD, as 'success' of at least 6 months on the diet can be obtained in elderly patients with high comorbidities and low educational level, further underlining the importance of individual choices and empowerment in CKD patients. Such a dietary programme is feasible, safe and adaptable to a routine clinical setting, and it can provide promising results in terms of slowing the progression of CKD, even though these results must be confirmed by studies using control groups and exploring its implementation in different clinical settings.

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(See related article by Thilly. Low-protein diet in chronic kidney disease: from questions of effectiveness to those of feasibility. *Nephrol Dial Transplant* 2013; 28: 2203–2205.)

REFERENCES

1. Berger A, Edelsberg J, Inglese GW *et al.* Cost comparison of peritoneal dialysis versus hemodialysis in end-stage renal disease. Am J Manag Care 2009; 15: 509–518
2. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005; 365: 331–340
3. Piccoli GB. Patient-based continuum of care in nephrology: why read Thomas Addis' 'Glomerular Nephritis' in 2010? J Nephrol 2010; 23: 164–167
4. Anonymous. The influence of a meat diet on the kidneys. Lancet 1907; 170: 1338
5. Blagg CR. Thomas Addis, 1881–1949, clinical scientist, hematologist and pioneering nephrologist: a brief biography. J Nephrol 2009; 22(Suppl 14): S115–S119
6. Bergstrom J. Discovery and rediscovery of low protein diet. Clin Nephrol 1984; 21: 29–35
7. El Nahas AM, Coles GA. Dietary treatment of chronic renal failure: ten unanswered questions. Lancet 1986; 327: 597–600
8. Giovannetti S. on behalf of the Steering Committee of the European Study Groups for the conservative treatment of chronic renal failure. Answers to ten questions on the dietary treatment of chronic renal failure. Lancet 1986; 328: 1140–1142
9. Fouque D, Aparicio M. Eleven reasons to control the protein intake of patients with chronic kidney disease. Nat Clin Pract Nephrol 2007; 3: 383–392
10. Walser M, Mitch WE, Maroni BJ *et al.* Should protein intake be restricted in predialysis patients? Kidney Int 1999; 55: 771–777
11. Walser M, Hill S. Can renal replacement be deferred by a supplemented very low protein diet? J Am Soc Nephrol 1999; 10: 110–116
12. Levey AS, Greene T, Beck GJ *et al.* Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? J Am Soc Nephrol 1999; 10: 2426–2439
13. Mitch W. Dietary protein restriction and progressive renal insufficiency. Am J Kidney Dis 1997;30: 297–298; discussion 299–300
14. Walser M. Is there a role for protein restriction in the treatment of chronic renal failure? Blood Purif 2000; 18: 304–312
15. Mitch WE, Remuzzi G. Diets for patients with chronic kidney disease, still worth prescribing. J Am Soc Nephrol 2004; 15: 234–237
16. Aparicio M, Chauveau P, De Précigout V *et al.* Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. J Am Soc Nephrol 2000; 11: 708–716
17. Chauveau P, Couzi L, Vendrely B *et al.* Long-term outcome on renal replacement therapy in patients who previously received a keto acid-supplemented very-low-protein diet. Am J Clin Nutr 2009; 90: 969–974
18. Mitch WE. Beneficial responses to modified diets in treating patients with chronic kidney disease. Kidney Int 2005; 67 (Suppl.94): S133–S135
19. Cianciaruso B, Pota A, Pisani A *et al.* Metabolic effects of two low protein diets in chronic kidney disease stage 4–5—a randomized controlled trial. Nephrol Dial Transplant 2008; 23: 636–644
20. Liou HH. What can a keto acid/amino acid-supplemented protein-restricted diet do for the 'butterfly effect' in chronic kidney disease patients? J Ren Nutr 2009; 19(5 Suppl): S15–S18
21. Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database Syst Rev 2009; (3): CD001892
22. Aparicio M, Bellizzi V, Chauveau P *et al.* Protein-restricted diets plus keto/amino acids—a valid therapeutic approach for chronic kidney disease patients. J Ren Nutr 2012; 22(2 Suppl): S1–S21
23. Anonymous. Diet and the progression of chronic renal failure. Lancet 1982; 320: 1314–1315
24. Mircescu G, Gârneață L, Stancu SH *et al.* Effects of a supplemented hypoproteic diet in chronic kidney disease. J Ren Nutr 2007; 17: 179–188
25. Lin S. New research areas for keto acid/amino acid-supplemented protein diets. J Ren Nutr 2009; 19(5 Suppl): S30–S32
26. Scalone L, Borghetti F, Brunori G *et al.* Cost-benefit analysis of supplemented very low-protein diet versus dialysis in elderly CKD5 patients. Nephrol Dial Transplant 2010; 25: 907–913

27. Aparicio M, Cano NJ, Cupisti A *et al.* Keto-acid therapy in predialysis chronic kidney disease patients: consensus statements. J Ren Nutr 2009; 19(5 Suppl): S33–S35
28. Winkelmayer WC, Weinstein MC, Mittleman MA *et al.* Health economic evaluations: the special case of end-stage renal disease treatment. Med Decis Making 2002; 22: 417–430
29. Mitch WE. Dietary therapy in uremia: the impact on nutrition and progressive renal failure. Kidney Int Suppl 2000; 75: S38–S43
30. Cooper BA, Branley P, Bulfone L *et al.* A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 2010; 363: 609–619
31. Stel VS, Dekker FW, Ansell D *et al.* Residual renal function at the start of dialysis and clinical outcomes. Nephrol Dial Tranplant 2009; 24: 3175–3182
32. Barsotti G, Morelli E, Cupisti A *et al.* A special, supplemented 'vegan' diet for nephrotic patients. Am J Nephrol 1991; 11: 380–385
33. Barsotti G, Morelli E, Cupisti A *et al.* A low-nitrogen low-phosphorus vegan diet for patients with chronic renal failure. Nephron 1996; 74: 390–394
34. Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 1985; 27: 58–65
35. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612
36. Piccoli GB, Attini R, Vasario E *et al.* Vegetarian supplemented low-protein diets. A safe option for pregnant CKD patients: report of 12 pregnancies in 11 patients. Nephrol Dial Transplant 2011; 26: 196–205
37. Piccoli GB, Motta D, Martina G *et al.* Low-protein vegetarian diet with alpha-chetoanalogues prior to pre-emptive pancreas-kidney transplantation. Rev Diabet Stud Summer 2004; 1: 95–102
38. Piccoli GB, Ferraresi M, Caputo F *et al.* Home hemodialysis and peritoneal dialysis compared. G Ital Nefrol 2012; 29: 148–159
39. Walker AE, Grimshaw J, Johnston M *et al.* PRIME-Process modeling in implementation research: selecting a theoretical basis for intervention to change clinical practice. BMC Health Serv Res 2003; 3: 22
40. Craig P, Dieppe P, Macintyre S *et al.*; Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008; 337: a1655
41. Di Iorio B, Di Micco L, Torraca S *et al.* Acute effects on very-low-protein diet on FGF23 levels: a randomised study. Clin J Am Soc Nephrol 2012; 7: 581–587

Piccoli and colleagues in Italy report on the tolerability, impact and outcomes of CKD4-5 patients (139) given a low protein diet (LPD) (0.6g/kg/day) supplement with keto-analogues (Ketosteril) compared to a standard LPD. They imply from their observation that such promising results on CKD progression and low mortality (4%/year) should encourage more to prescribe such a diet to patients with advanced renal insufficiency.

This observational cohort study is a throw back to the 70-80s when such diets including those with a very low in protein content (0.3g/kg/day) were prescribed to patients with advanced renal insufficiency, mainly by Italian Nephrologists to delay the onset of dialysis.

Since, a group of like-minded nephrologists came to the "final" conclusion that such diets are potentially beneficial [1]. The validity of their argument remains to be tested! In The UK, such diets are seldom recommended.

(1) Are Italian nephrologists still prescribing LPDs to patients with CKD4-5, in spite of the negative result of the MDRD largest randomized controlled study published in 1994 [2]?

(2) How can CKD progression be evaluated on such diets with serum creatinine, creatinine clearance or creatinine derived equations knowing that such diets impact on creatine intake, metabolism, stores as well as urinary excretion? This is a point acknowledged by the authors, but of concern to the NDT OLA readers as such diets give the subjective impression of functional improvement and delay of the onset of ESRD and RRT when in reality they alter an inappropriate surrogate marker for CKD, namely serum creatinine, under such dietary prescription! This brings back my old Lancet review highlighting 10 unanswered question with LPD ….[3]. Although these questions, were challenged by Fouque and Aparicio by 11 arguments … as to why such diets should be prescribed [4]. I remain unconvinced!

(3) What is the true risk:benefit and cost:benefit analyses of such diets in terms of nutritional status and outcomes when compared to a free protein intake which is known to be spontaneously reduced in advanced renal insufficiency ?

(4) Finally, how can such dietary protein restrictions be justified in low and middle economies where undernutrition is a feature of ESRD?

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REFERENCES

1. Aparicio M, Bellizzi V, Chauveau P, Cupisti A, Ecder T, Fouque D, Garneata L, Lin S, Mitch WE, Teplan V, Zakar G, Yu X. "http://www.ncbi.nlm.nih.gov/pubmed/22365372" Keto acid therapy in predialysis chronic kidney disease patients: final consensus. J Ren Nutr. 2012 Mar;22(2 Suppl):S22–4.
2. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. "http://www.ncbi.nlm.nih.gov/pubmed/8114857" The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994 Mar 31;330(13):877–84.
3. El Nahas AM, Coles GA. "http://www.ncbi.nlm.nih.gov/pubmed/2869311" Dietary treatment of chronic renal failure: ten unanswered questions. Lancet. 1986 Mar 15;1(8481):597–600.
4. Fouque D, Aparicio M. "http://www.ncbi.nlm.nih.gov/pubmed/17592471" Eleven reasons to control the protein intake of patients with chronic kidney disease. Nat Clin Pract Nephrol. 2007 Jul;3(7):383–92.

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