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ADHERENCE AND OUTCOMES OF THE LOW AND VERY LOW PROTEIN DIETS IN CHRONIC DIABETIC KIDNEY DISEASE – A DEBATE THAT NEEDS CONSENSUS

Ileana Teodoru [1,✉], ***Iulian Mincu*** [2], ***Gabriela Radulian*** [2]

[1] National Institute of Diabetes, Nutrition and Metabolic Diseases „Prof. N. C. Paulescu", Compartment of Nephrology (Nephrology Department)
[2] National Institute of Diabetes, Nutrition and Metabolic Diseases „Prof. N. C. Paulescu", Diabetes 2nd Clinic

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Abstract

Since the Brenner`s theory of the „workload" in the remnant nephrons, due to the largely available access to the dialysis facilities, many patients with advanced chronic kidney disease (CKD) were given low-protein diets (LPDs) apparently with great success. Four main diets are today accepted for achieving a balanced intake of 0.6 g protein/kg/day diet and together with a very low-protein diet of 0.3 g protein/kg/day with keto-analogues and amino-acids supplementation, known as keto-diet, are recommended in specific situations. Still, some questions have debatable answers and are waiting for more conclusive studies: are low and very low-protein diets (VLPDs) really effective in diabetic CKD?; which LPD should be given? and what strategy should be used in order to get maximum compliance and best outcomes?

key words: *LPD and VLPD diets, diabetic CKD patients, consensus.*

Introduction

Since the Brenner`s theory of the „workload" in the remnant nephrons, to the paper of Giovanetti and Maggiore published in the Lancet 50 years ago [1], many patients with advanced chronic kidney disease (CKD) were given low-protein diets (LPDs) apparently with great success. Later on, the popularity of such diets decreased dramatically while being confronted with the spectrum of malnutrition and with the moment when dialysis facilities became largely available. Starting dialysis earlier became an attractive approach in reducing mortality and morbidity in CKD. Studies demonstrated that diabetic CKD patients might need hemodialysis earlier than the non-diabetic ones, and the costs with the progression of CKD from stage 3a to stage 5ND (not dialysed) in patients with type 2 diabetes mellitus (T2DM) are higher than in the non-diabetic patients, so the restricted protein diets became once again attractive [2,3]. Still, some questions have debatable answers and are awaiting for more conclusive studies: are low and very low-protein diets (VLPDs) really effective in diabetic CKD?, which low-protein diet (LPD) should be given? and what strategy should be used in order to get a maximum

✉ Ion Movila 5-7,sector 2 Bucharest,Romania; Tel.0721227960
corresponding author e-mail: teodoruileana@yahoo.com

compliance and the best outcomes for the patients?

What is „normal" and what are „low-protein diets" (LPDs)?

The FDA (Food and Drug Administration) Reference Daily Intake or Recommended Daily Intake of proteins is the daily intake that suffices to meet the requirements of 97-98% of healthy individuals in every demographic, which in the USA and most Western European countries is about 0.8 g/kg/day of proteins, different from the 1.0 g/kg/day formerly identified as „normal" [4-6]. Consequently, what we used to call LPD (0.6 g/kg/day) is today a moderately restricted protein diet, as far as 0.8 g/kg/day became the „normal"diet.

The different levels of protein restriction were tested using various definitions: initially according to the total protein content of the diet (40 g proteins versus 18-20 g proteins), and later expressed as g per kg body weight per day (g/kg/d).The „safety interval"of protein restriction could be defined by the early studies somewhere between the lowest safely achievable protein intake of 0.3 g/kg/day supplemented with essential amino-acids and keto-analogs of amino-acids, and the upper level of protein restriction that has a measurable effect on CKD progression of 0.6 g/kg/day [1,7-17]. These LPD-studies could calculate a 1 year prolongation of lifespan without dialysis, with better effects when started earlier [10-16].

In order to see whether we could achieve almost as much by changing the type of protein in the diet, rather than the amount, some studies demonstrated a favorable effect of soy proteins in experimental animals, kidney transplanted patients and diabetic patients [18-21]. Pecis et al. compared three diets: usual hyperproteic (high protein) diet (1.4 g/kg/day), LPD (0.5 g/kg/day) and the diet in which chicken and fish replaced red meat. The results suggested that chicken-fish diet had similar effects on glomerular filtration rate (GFR) as the LPD, being of course a more friendly diet. The authors considered that the obtained results are due to the much lower levels of glycine, alanine and arginine in chicken and fish meat, compared with the red meat [22]. The latest amino-acids mentioned are believed to have the greatest impact on GFR. Anyway, this was a short 3-weeks study, so larger and long-term studies are needed for further conclusions.

As highlighted in a recent *Clinical Kidney Journal* review by Piccoli et al., the four main policies for achieving a balanced 0.6 g/kg/day protein diet are: traditional, vegan, vegan-supplemented and vegan with protein-free food [23]. It is generally accepted that moderate protein restriction is feasible without the need for supplements or protein-free food.

1. **The traditional** Mediterranean diets integrate vegetables and cereals and a very small amount of dairy products or meat – fish, which supplies the essential amino-acids. The Okinawa diet adds very small amounts of animal proteins to a diet based on fruits and vegetables. When baseline diet is less rich in vegetables and cereals, as in the world of fast-food of Western countries, diet „adaptation" can be sometimes impossible.

2. **Vegetarian diets** are free from „living" sources of food (fish, meat and poultry) and can be divided into „strict" (corresponding to the current vegan diets) and other variants, including ovo-vegetarian (plus eggs), lacto-vegetarian (plus milk and dairy-products), or pescetarian (plus fish). Vegan-vegetarian diets contain vegetable proteins, less enhancing renal hyper-filtration since vegetable proteins are less available than animal proteins and are considered safe in all periods of life and phases of human development by most respected associations and prominent scientists [24-30]. Non-restricted vegan diets usually provide a

0.6-0.8 g/kg/day protein intake with the gold-standard of combining at every meal a high variety of vegetables and cereals and/or soy products to ensure the proper intake of essential amino acids. Best examples in literature are known as Barsotti and Soroka diets [28,29,31].

3. **The vegan 0.6 g protein diets supplemented with amino-acids and keto-acids** may be useful when the omnivorous patients are abruptly getting a vegan regimen, or when the patient doesn`t tolerate vegetables. The supplementation allows a simplified approach that leaves a free choice of vegetables, fruits and cereals, excluding any animal-derived food. This could be an excellent strategy for diabetics, pregnant women or patients on recovering renal function. The dose of supplements in the 0.6 g protein/kg/day diet is not standardized, but the usual prescription is 1 pill/ 10 kg/day [32-37].

4. **The vegan 0.6 g protein diets with protein-free food** is difficult to apply**.** Natural protein-free foods (tapioca, butter, sugar, fruits and vegetables) can offer only a relatively monotonous diet. The first protein-free pasta was produced in 1966, followed in the late `70s by industrial production of pasta, flour, bread, biscuits and more recently protein-free snacks, partially cooked food and drinks, that became available to everyone interested [38]. If usual cereals are replaced with protein-free foods, the patient can achieve a high caloric intake having at the same time more freedom for planning the rest of the diet. This type of diet is preferred by people of the Mediterranean countries (where bread and pasta offer half of daily proteins, about 12 g protein/100 g product). Calorie-rich foods can be added to this (maltodextrin and oil creamer) to avoid malnutrition [39,40]. Unfortunately, protein-free foods are available free of charge to CKD patients only in Italy, limiting the general use of such diets [33].

The very low-protein diet (VLPD), usually meaning 0.3 g protein/kg/day, requires a supplementation of amino-acids and keto-acids, conventionally established as a necessary of 1 pill/5 kg/day. Presently, only two combinations of amino-acids and keto-acids are available: Alpha Kappa® in Italy and Ketosteril®, all over the world [41,42]. The difference between their composition consists in the presence of 23 mg L-tryptophan/pill in Ketosteril®. In the absence of any clearly demonstrated clinical difference, they are considered equivalent and interchangeable (Table 1) [32,33,45]. The combination of vegan diet together with commercial protein-free food and a considerable amount of supplements/pills makes the VLPD a kind of „artificial diet", not easily accepted and kept by the patients. But despite these difficulties, VLPDs are usually considered more effective in postponing dialysis in compliant patients and they may have a specific indication in the rescue treatment of nephrotic syndrome resistant to the therapies specifically addressing the pathophysiologic mechanisms [43,44]. Further on, there are concerns about how to improve compliance to such diets, as far as the actual menu of these diets is missing in the literature. There are various strategies proposed: while some studies used a qualitative simplification of the diet based upon forbidden and allowed food for the vegan diets, or upon substitution of carbohydrates with protein-free food [32-37], others applied a policy of occasionally unrestricted meal (one to three times/week), or one day a week off-diet. Two study groups have systematically reported inclusion of free meals, in order to obtain good compliance [32-37,39]. Another concern in these already restricted VLPDs is the importance of added polyphosphates and also the sodium and potassium content, because the list of potentially toxic additives is quite large and their effect on the evolution of CKD has not yet been thoroughly investigated.

Table 1. Comparison of the daily amino-acids, keto-acids and calcium requirements recommended by World Health Organisation (WHO) and the daily intake of amino-acids, keto-acids and calcium with Ketosteril® - supplementation (1 tablet/5 kg) [45].

Keto/Amino-Acids	Requirements in Adults		Ketosteril®		% WHO
	mg/kg/day	mg/60 kg/day	(mg/tabl.)	60 kg (12 tabl./day)	
Isoleucine	10	600	58	696	116
Leucine	14	840	87.4	1.049	125
Valine	10	600	73.2	878	146
Phenylalanine+ +Tyrosine	14	840	$90.5_{Tyr+Phe}$	1.086	129
Ornithine	-	-	-	-	-
Histidine	8-12	480-720	38	456	76
Lysine	12	720	75	900	125
Methionine+Cystine	13	780	52_{Met}	624	80
Threonine	7	420	53	636	151
Tryptophan	3.5	210	23	276	131
Calcium	800-1.200	50	600	60	

Are LPD and VLPD really useful?

The natural history of diabetic nephropathy shows invariable progression even though at different rates: without treatment the decline in GFR has been reported to be of 9-14 ml/min/year in type 1 diabetes mellitus (T1DM) with proteinuria, but slower in patients with type 2 diabetes mellitus (T2DM) and nephropathy ~ 6 ml/min/year. There was also reported that patients with T2DM developed proteinuria earlier, but progressed more slowly [46].

The largest randomized controlled trial on diet in kidney disease, the Modification of Diet in Renal Disease (MDRD) study failed to demonstrate an advantage in the primary intention-to-treat analysis, but still supported a positive effect in the secondary per-protocol analyses and highlighted the crucial role of compliance in chronic diseases, adding also two very important and useful tools of monitoring CKD: the MDRD equation for GFR assessment and the only dietary satisfaction questionnaire validated in kidney patients [23].

Boner and Cooper, in their „Management of Diabetic Nephropathy" [46], reviewed the studies which have examined the effects of dietary protein restriction in diabetic patiets. They have included both randomized control trials (RCTs) and "before and after" studies. Because creatinine clearance takes at least 3 months to reach equilibrium, they excluded from the beginning all the studies with a duration of less than 4 months, and also those in which changes in other treatments, particularly anti-hypertension drugs, confounded the results. They used GFR as the main outcome measure. Both T1DM and T2DM studies were included, covering a period from 1997 to 2000 with no study size restrictions. The authors looked for details in the compliance measurements using biological methods rather than self-reporting. Nearly all the trials demonstrated the fact that protein restriction slows the decline of renal function. In the LPD sample of T1DM studies, the average decline was 11 ml/min/year, less than in usual protein diets (UPD). Since the usual decline in GFR is about 10 ml/min/year, a patient on LPD may delay the onset of dialysis by around 10 months to 1 year (Table 2) [46].

The study by Pijls and colleagues [50] in T2DM patients (not shown in the table) gave disappointing results because the patients did not comply with the diet, but Walker et al. [51] and Zeller et al. [52] studies in T1DM showed that compliance is possible for most patients over 3

years, although they used a milder protein restriction than in other short-term studies. Both short and long-term studies showed great benefits, with follow-up of 2 or more years. Long-term studies are probably more representative of what happens on routine care, with an average reduction of the GFR decline of about 8 ml/min/year. In the study of Walker et al., 19 patients were included, but four were started on antihypertensive treatment while on the low-protein diet; these patients have been excluded from the analysis presented shown in table 2. The given diets were as described above. In the study of Pijls et al. [50], compliance was poor and the true difference in protein intake was of only 0.03 g/kg/day at 12 months. Trials about protein restriction in T1DM are consistent in showing a slower progression of CKD [46]. There is no good evidence concerning efficacy of LPD in type 2 diabetes due to the low diet compliance in the Pijls et al. study [50].

Table 2. Low-Protein Diet Studies (adapted after [46]).

Study	Number of. patients	Design	UPD (Usual protein diet) g/Kg /day	LPD (Low protein diet) g/Kg /day	Duration	GFR change UPD ml /min/ Month	GFR change LPD ml /min/ Month	Difference	GFR Decline (Reduction / Year)
Barsotti et al. 1988 [47]	8 Type 1	Before & After	> 1.2	0.3 vege-tarian	11 Months	-1.48	-0.13	1.33	16 ml/min
Barsotti et al. 1998 [48]	32&22 Type 1	Before & After	Not Started	0.3 or 0.7	2-8 Years	-0.9	-0.22	0.68	8.2 ml/min
Brouhard & La Grone 1990 [49]	15 Type 1	RCT	1.0	0.6	12 Months	-0.68	0.28	0.4	4.8 ml/min
Walker et al. 1989 [51]	15 Type 1	Before & After	1.13	0.67	33 Months	-0.54	-0.17	0.37	4.4 ml/min
Zeller et al. 1991 [52]	35 Type 1	RCT	1 or More	0.6	35 Months	1.0	0.26	0.74	8.9 ml/min

Hansen et al. [53] reported the largest randomized trial in diabetic patients treated with insulin, in which patients were given their usual protein diet or a 0.6 g protein/kg/day for a 4 year period. Actual protein intake was 1.02 g protein/kg/day versus 0.89 g/kg/day. No differences in proteinuria were observed, but death of renal causes was reduced by 36% in patients treated with moderately restricted protein intake. Cox analysis was performed after adjusting for cardiovascular diseases and the difference was even more significant (p=0.01). In a meta-analysis of a subgroup of patients with diabetes, Pedrini et al. showed that a combined criterion of increasing microalbuminuria and decreasing renal function was improved by 44% ($p<0.001$) in subjects assigned to a LPD [54].

What about malnutrition and VLPD?

Patients with CKD secondary to diabetes mellitus have higher incidences of malnutrition as compared with non-diabetic subjects: concomitant illnesses, poor glycemic control, the higher occurrence of nephrotic syndrome, gastroparesis, diabetic diarrhea are all possible causes of muscle loss and functional impairment in diabetic patients. In addition to the abnormalities resulting from the elevated blood

urea, diabetics have multiple endocrine abnormalities, including insulinopenia or insulin resistance and increased cortisol, glucagon and epinephrine, which could per se induce catabolism or cause an impairment in the response to a low nutrient intake. Therefore, wasting syndrome in patients with diabetic CKD may occur as the result of the overlapping abnormalities in the metabolic control of protein turnover that are particular to diabetes and uremia.

Still, CKD patients are able to adapt to marked dietary protein restriction with simultaneous substitution of essential amino-acids and their keto-analogues; the neutral nitrogen balance is achieved by a marked suppression of the amino-acid oxidation and postprandial inhibition of protein degradation, so that the DEXA evaluation of body composition confirms the long-term safety of VLPD supplemented with keto-analogues. Also, indirect data suggest that the mechanisms by which protein turnover adapts to a LPD can be impaired in the presence of metabolic acidosis [55]. More than that, the protein metabolism and N-balance adapt successfully in patients who are compliant to VLPD supplemented with keto-analogues of amino-acids in non-acidotic CKD patients.

Beneficial effects of dietary protein restriction on glucose metabolism have been reported in diabetic patients without uremia. Indeed, several investigators indicated there is no further requirement of insulin in diabetic patients who follow a VLPD supplemented with keto-analogues, in spite of the increased amount of carbohydrates administered to maintain a satisfactory energy intake of 30-35 kcal/kg/day, during treatment. Furthermore, Gin et al. [56] demonstrated an improvement of insulin sensitivity by using the euglycemic clamp technique. This improvement in insulin sensitivity might compensate the carbohydrate excess of the diet with no negative effect on the insulin needed.

Concerning the nephrotic syndrome, the mechanisms by which these patients lose muscle mass are not fully understood; in such patients the whole protein degradation and synthesis are not increased and the mechanisms to reduce nitrogen losses are activated properly when nitrogen intake is reduced, therefore malnutrition in nephrotic patients is mainly the result of anorexia [43,44]. In the study of Maroni et al. [57], when protein intake was restricted, the principal compensatory response was a decrease in amino-acid oxidation; with the LPD, leucin oxidation rates were inversely proportional to the proteinuria, suggesting that proteinuria is a stimulus to conserve dietary essential amino-acids. Therefore, these data demonstrate that nephrotic syndrome patients activate normal responses to dietary protein restriction and feeding.

So, the main outcome of a LPD or a keto-analogue amino-acid supplemented VLPD on the diabetic nephropathy is the slowing down of GFR-decline, the reduction of urinary protein-loss and the improvement of secondary hyperparathyroidism, as well as renal osteodystrophy (in the absence of protein phosphorus intake, the calcium salt presentation of keto-analogues act as a phosphate binder, resulting in formation of insoluble calcium phosphates in the intestine - an anti-absorbent action).

Discussions

When the effectiveness of the dietary intervention depends on the subject`s active participation, and on the reflection of patient`s preferences, a randomized trial might be inappropriate because the very act of random allocation may reduce the effectiveness of the dietary intervention. Thus while randomized

controlled trials (RCTs) are best for studying short-term efficacy, observational studies may be more appropriate for analyzing their implementation and highlighting the interactions with patient`s preferences and compliance [23]. RCTs and the observational studies have complementary roles. Observational studies may extend evidence over a wider population and are likely to be dominant in the identification of harms and when RCTs would be unethical or impractical. One may design a multiple choice diet system with easy access to different options so that each patient may find the best diet, or at least the less intrusive one [23].

A stepwise option, starting from moderate protein restriction, could be proposed to all patients with progressive or advanced CKD in the attempt to allocate each patient to the simplest and most feasible diet option (such as simplified vegan diets for youth, traditional and protein-free food for elderly), while strict VLPDs will probably play a role in highly motivated, well-trained patients, or in selected patients, for whom postponing dialysis may be of particular relevance [23]. VLPD supplemented with keto-analogues of amino-acids (keto-diet) seems to be a promising nutritional tool in the therapeutic arsenal, even in diabetic patients with advanced CKD and nephrotic syndrome. It should be considered in selected patients, without severe gastrointestinal disturbances or other severe catabolic conditions and acidosis, mandatory provided with sustained nutritional assistance, according to their energetic needs and comorbidities and with an adequate psychological advice, suited to their personality profiles. The golden standard for success in patient compliance should take into account the NDNP –formula with a nephrologist, diabetologist, nutritionist and psychologist working together and completing each other, same as the vital elements of life (earth, air, water and fire), in order to maximize the outcome of the treated patients on diet. Discussions between nutritionist and patient should be finalized with concrete examples of menus for 7-14 days and involve permanent efforts of a psychologist to adapt life habits of the patient to the new morbid condition rather than simply restrict consumption of one or another food. Also, the patient should be convinced about his/her new chance to live without dialysis rather than underline the new dietary restrictions.

Conclusions

Considering that the overall health costs per patient per year on these diets in predialysis are much smaller than those for patients on substitutive methods (with all possible complications related), and that slowing down CKD progression is preferred to keep patients professionally and socially active, productive and independent of dialysis, any effort to promote and improve a keto-diet might be worthy. In the future, cheaper production technologies will improve accessibility to protein-free products and keto-analogues, so that there should be no economic limitation for using such products in all eligible patients. These products, in combination with vegetal proteins and adequate caloric intake, may even reverse incipient diabetic CKD, or gain years, possibly decades, until entering a renal replacement method.

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