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Protein restriction and chronic kidney disease

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Abstract

Background: Experimental evidence suggests that protein restriction can ameliorate glomerular hyperfiltration and preserve glomerular filtration rate (GFR), but not all clinical studies demonstrate consistent beneficial effects in all patients with chronic kidney disease (CKD), questioning its safety about diminished energy intake and risk of malnutrition. The authors aim to perform a comprehensive review of the effectiveness and safety of protein restriction on CKD progression.

Methods: The present work includes articles published on PubMed from 2000 up to 2023, analyzing the effect of protein restriction on CKD progression among patients with CKD stages 3, 4 and 5, not on dialysis. The analyzed outcome of CKD progression (GFR decline or end-stage renal disease (ESRD) occurrence) was defined accordingly in each study.

High dietary protein intake leads to increased intraglomerular pressure and glomerular hyperfiltration, which in the long-term will be harmful for the kidneys. Thus, lowering protein intake in CKD patients is a recommended measure by the recent international guidelines by KDOQI and several studies showed favorable effects on delaying GFR decline or ESRD occurrence rates. Therefore, it seems reasonable to follow a well-designed protein-restricted diet on CKD patients between stages 3, 4 and 5 (not on dialysis) to delay progression of CKD. In these patients, the concern with malnutrition was not proved. Concluding that restricting protein in diet needs to be balanced with a concomitant adequate energy intake to sustain dietary management safety.

Key-words: chronic kidney disease, protein restriction; chronic kidney disease, low-protein diet; chronic kidney disease, protein intake; chronic kidney disease, nutrition; chronic kidney disease progression, protein restriction.

Resumo

Introdução: Há evidência experimental sugestiva de que a restrição proteica pode melhorar a hiperfiltração glomerular e preservar a taxa de filtração glomerular (TFG), mas nem todos os estudos clínicos demonstram efeitos benéficos consistentes em todos os pacientes com doença renal crónica (DRC), questionando a sua segurança sobre a diminuição do consumo energético e o risco de malnutrição. Os autores pretendem realizar uma revisão abrangente da eficácia e segurança da restrição proteica na progressão da DRC.

Métodos: Esta revisão narrativa inclui artigos publicados no PubMed, entre 2000 e 2023, sobre o efeito da restrição proteica na progressão da DRC em pacientes com DRC nos estágios 3, 4 e 5 sem diálise. A análise do efeito da progressão da DRC (declínio da TFG ou ocorrência de insuficiência renal terminal (IRT)) foi definida de acordo com cada estudo.

A ingestão elevada de proteínas na dieta leva ao aumento da pressão intraglomerular e à hiperfiltração glomerular, que a longo prazo será prejudicial para os rins. Assim, a restrição proteica em pacientes com DRC é uma medida recomendada pelas recentes diretrizes internacionais KDOQI, e vários estudos têm demonstrado efeitos favoráveis na diminuição do declínio da TFG ou nas taxas de ocorrência de IRT. Assim sendo, parece aconselhável seguir uma dieta com restrição proteica bem estruturada em pacientes com DRC entre os estágios 3, 4 e 5 (sem diálise) para retardar a progressão da DRC. A preocupação com a ocorrência de malnutrição nestes doentes não foi comprovada. Concluindo que uma dieta com restrição proteica precisa de uma ingestão energético calórica adequada concomitante, para manter a segurança destas medidas.

Palavras-chave: doença renal crónica, restrição proteica; doença renal crónica, dietas hipoproteicas; doença renal crónica, nutrição; doença renal crónica, ingestão proteica; progressão da doença renal crónica, restrição proteica.

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Background

Chronic Kidney Disease (CKD) results from progressive and irreversible damage to the kidneys and has been recognized as a leading public health problem worldwide, affecting more than 10% of the general population, amounting to more than 800 million individuals. By 2030, the number of patients requiring dialysis is estimated to double, reaching 5.4 million patients, mostly in the developing countries (Kovesdy, 2022). The current international guidelines define CKD as the presence of abnormalities of kidney structure or function, namely decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2, or markers of kidney damage (albuminuria>30 mg/g, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology or imaging and history of kidney transplantation), or both, for at least 3 months and it is classified in different stages according to GFR and albuminuria (KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, n.d.).

Regardless of the underlying etiology (diabetes, hypertension, toxin exposure, immune complex deposition, autoimmune diseases, etc.), glomerular hypertension and hyperfiltration are known to be major contributors to the development and progression of CKD (Webster et al., 2017).

High protein intake results in vasodilation of the afferent arterioles in the glomerulus, which increases intraglomerular pressure and leads to hyperfiltration. Sustained intraglomerular hypertension increases mesangial matrix production and leads to glomerulosclerosis by extracellular matrix accumulation and irreversible loss of nephrons, which further increases flow to the remaining glomeruli in a self-perpetuating vicious cycle (Matovinović,2009). Experimental evidence suggests that protein restriction can ameliorate glomerular hyperfiltration and preserve GFR, but not all clinical studies demonstrate consistent beneficial effects in all patients with CKD, questioning its safety about diminished energy intake and risk of malnutrition.

This is a comprehensive review on the effectiveness and safety of protein restriction on CKD progression.

Materials and Methods

For this narrative review, we conducted the following literature searches through PubMed search engine with the MeSH terms: 1) chronic kidney disease, protein restriction; 2) chronic kidney disease, low-protein diet; 3) chronic kidney disease, protein intake, 4) chronic kidney disease, nutrition, 5) chronic kidney disease progression, protein restriction.

Inclusion criteria were articles published in English from 2000 to 2023, including patients with CKD stages 3 to 5 under various degrees of dietary protein intake.

The Kidney Disease Quality Outcomes Initiative (KDOQI) guidelines on nutrition in CKD patients define low-protein diet (LPD) as an amount of 0.55-0.60 g of protein/kg of body weight/day, very low-protein diet (VLPD) as an amount of 0.28-0.43 g of protein/kg of body weight/day with additional keto acid (KA) or essential amino acid (EAA) analogs to meet protein requirements (0.55–0.60 g of protein/kg of body weight/day), and normal protein diet (NPD) as more than 1.1 g of protein/kg of body weight/day (Ikizler et al., 2020).

The analyzed protein diet and outcome of CKD progression was defined accordingly in each study.

Protein Intake and Kidney Function

A high-protein load has been reported to increase glomerular filtration (GF), through a feedback mechanism that leads to afferent artery vasodilation, which facilitates the excretion of increased amounts of protein-derived nitrogenous products (Kalantar-Zadeh K, 2016;17:90; Ko et al., 2020; G.-J. Ko & Kalantar-Zadeh, 2021).

Models for high protein-induced hyperfiltration have been well reported primarily in animal experiments (Tanaka et al., 2023) and later in human studies (G. J. Ko et al., 2017;

G.-J. Ko et al., 2020; G.-J. Ko & Kalantar-Zadeh, 2021). In 2014, an ancillary study of the Omni Heart trial revealed that a high-protein diet increased GFR by 3.8 mL/min/1.73 m^2 after 6 weeks (Juraschek et al., 2013). Adding to that, a meta-analysis including 30 randomized clinical trials (RCTs) with 1599 patients also confirmed a median increase of 7.18 mL/min/1.73 m^2 in GFR in those submitted to a normal/higher protein diet ($p<0.001$) (Schwingshackl & Hoffmann, 2014).

Whereas the GFR may increase in the short term, kidney damage may ensue, and the renal function will deteriorate over time (G. J. Ko et al., 2017). Sustained and prolonged hyperfiltration ultimately leads to kidney fibrosis and failure through multiple pathways (Kalantar-Zadeh et al., 2019; Kitada et al., 2018). Glomerular hyperfiltration induces mesangial cell production of transforming growth factor-β (TGF-β), which subsequently contributes to the progression of kidney fibrosis by stimulating extracellular matrix production, while inhibiting its degradation (Panizo et al., 2021). Plus, in Diabetic Kidney Disease (DKD), the accumulation of advanced glycation end products (AGEs) contained on protein-rich foods, such as meat cooked at high heat, (Goldberg et al., 2004) impairs protein degradation, which leads to basement membrane thickening and mesangial expansion in glomerulus. This pathogenic response of AGEs is mediated by a proinflammatory receptor (RAGE), present in glomerular cells, and culminates in cellular inflammation and death (G.-J. Ko & Kalantar-Zadeh, 2021).

Several studies have reported a decline in GFR in participants who followed a high-protein diet. In the *Nurses' Health Study*, 1624 participants were followed up for more than 10 years. Every 10-gram increase in protein intake was associated with a decrease in GFR of −1.69 mL/min/1.73 m^2 (18). In a recent observational study conducted by Jhee et al, the highest protein intake group was associated with a 3.48-fold higher risk of hyperfiltration, which was also associated with a more than 3mL/min/1.73 m^2/year decrease of GFR (Jhee et al., 2019).

Considering the effects of a high protein intake on hyperfiltration and consequent GFR decline, it is hypothesized that a restriction on the protein intake could delay progression of CKD through opposite mechanisms. Lowering protein intake leads to

greater constriction of the afferent arteriole, reducing the GFR and kidney workload, which might be renoprotective (Kalantar-Zadeh & Fouque, 2017).

Effect of Protein Restriction in Slowing CKD Progression

The recent KDOQI guidelines on nutrition recommend lowering protein intake in stages 3 to 5, when patients are metabolically stable, supported by several systematic reviews and meta-analysis of well-designed clinical trials (Ikizler et al., 2020).

The largest study analyzing the effect of protein restriction on CKD patients was the Modification of Diet in Renal Disease (MDRD) Study. This study consisted of two RCTs: study A, conducted in moderate renal disease (GFR 25 to 55 mL/min/1.73 m^2), in which patients were prescribed an NPD or an LPD, 1.3 or 0.58 g/kg/day of protein, respectively; and study B, conducted in advanced renal disease (GFR 13 to 24 mL/min/1.73 m^2), in which patients were assigned to an LPD or a VLPD, containing 0.28 g/kg/day of protein, supplemented with KAs and EAAs. In study A, GFR decline was 28% less in the LPD group after the first four months (p=0.009), although, overall, the decline in GFR was only 1.2mL/min less than the NPD group (p=0.3). In study B, VLPD had a 95% slower mean GFR decline (p=0.07), nevertheless it did not translate into reduced incidence of ESRD or death. Therefore, the beneficial effect was not demonstrated.

Numerous secondary analyses of the MDRD Study (Levey A.S,. 2006, n.d.; Menon V., 2009; n.d.) were performed to ascertain the clear effect of protein restriction on the rate of GFR decline and more recent studies report a beneficial effect of LPDs on improving CKD prognosis (Baragetti et al., 2020; Brunori et al., 2007; Cianciaruso B, Pota A, Bellizzi V, et al. .; Eyre et al., 2008; Garneata et al., 2016; Ideura et al., 2003; Meloni et al., 2004; Mircescu et al., 2007; Otani et al., 2023; Prakash et al., 2004; Satirapoj et al., 2018; Teplanl et al., n.d.).

In a prospective cohort of 105 patients, Teplan et al demonstrated that an LPD of 0.6 g/kg/day and supplementation of KAs had the lowest decline in GFR decline (p<0.01)

(Teplanl et al., n.d.). Four more recent retrospective studies demonstrated that non-supplemented LPD therapy was also effective on delaying CKD progression (Baragetti et al., 2020; Eyre et al., 2008; Ideura et al., 2003; Otani et al., 2023).

Ideura et al. presented a significant improve in GFR decline in the LPD group (-7.2 mL/ min vs. -0.2 mL/min, $p<0.001$) compared to the control group, within only 3 months. One year after LPD prescription, 58% participants of the LPD group are still on predialysis treatment and 10% of patients delayed dialysis therapy for more than 5 years. In contrast, all patients in the control group were initiating dialysis within 6 months after the beginning of the study (Ideura et al., 2003). Later, Eyre et al. recruited CKD patients treated with an LPD or an NPD six months before initiating dialysis and investigated the effects of protein restriction not only on renal function, but also on morbidity and mortality outcomes. The mean rate of GF progression before dialysis admission was lower in the LPD group (-4.1mL/min/year) than in the control group (-13.4 mL/min/year) ($p<0.001$), but there was no difference in mortality between groups, either 1, 2, or 5 years after starting dialysis ($p<0.001$) (Eyre et al., 2008).

Recently, Baragetti et al showed that individuals affected by severe CKD had a larger decrease in GFR when submitted to an LPD versus an unrestricted one (-2.9 mL/min/1.73 m^2 vs. -6.0 mL/min/1.73 m^2, $p=0.018$). Plus, there even was an increase in GFR of 0.36 mL/min/1.73 m^2 ($p=0.001$) in the controlled protein diet (CPD) group, where an amount of 0.8 g of protein/kg/day was implemented. Restricting protein was also effective in postponing dialysis, since LPD and CPD patients began dialysis with a delay of 24 and 21 months, respectively, when compared with the NPD patients ($p< 0.001$ and $p=0.003$, respectively) (Baragetti et al., 2020). In the current year, a multicenter cohort study undertaken in Japan suggested that a non-supplemented LPD of 0.5 g/kg/day or less was associated with a significant delay on RRT initiation ($p=0.042$) and a lower mortality risk on CKD patients (Otani et al., 2023).

Furthermore, two recent RCTs also evaluated the effects of protein restriction with no supplementation on CKD progression (Cianciaruso B, Pota A, Bellizzi V, et al., n.d.; Meloni et al., 2004).

In 2009, Cianciaruso et al conducted an RCT, including more than 400 participants with CKD stages 4 and 5, and compared the effects of LPDs as opposed to moderate-protein-diets (MPDs) on the long-term survival of these patients. The LPD group (0.55 g/kg per day) did not have a survival advantage compared with the MPD group (0.80 g/kg per day), since no significant differences on GFR or dialysis start were observed (Cianciaruso B, Pota A, Bellizzi V, et al.. 2009;54:1052–1061, n.d.). The most important limitation of this study is related to the secondary nature of the analysis. The study hypothesis was tested using data from a randomized trial (Cianciaruso et al., 2008) powered to test another hypothesis related to metabolic and laboratory outcome measures.

In 2004, Meloni et al performed an RCT where the participants were divided into a non-diabetic and a diabetic group. Each group was further divided into two new groups, which were then submitted to either an LPD or a normal one. In the non-diabetic group under an LPD intake, a lower decrease of renal function was observed ($p<0.001$) and the diabetic group had no significant differences between the treatment group and the control group (Meloni et al., 2004).

A 2018 critical review and meta-analysis of 16 RCTs compared normal to restricted protein intake of less than 0.8 g/kg/day and demonstrated a 4% lower risk of progression to ESRD in those who received LPDs ($p=0.153$) (Rhee et al., 2018).

When it comes to DKD, one of the main causes of CKD and a significant risk factor for ESRD, the abovementioned positive effect of LPDs is not observed in such patients (Dussol et al., 2005; Hansen et al., 2002; S. Jiang et al., 2023; Koya et al., 2009; Li et al., 2019; Nezu et al., 2013; Pan et al., 2008; Pijls et al., 2002; Zhu et al., 2018).

Four prospective RCTs featuring only diabetic participants were presented (39,46). Firstly, in 2002, Meloni et al conducted a prospective RCT including 69 CKD stage 4 patients with type I and II diabetes and neither demonstrated any significant differences on renal outcomes (Meloni et al., 2002). Secondly, Dussol et al. performed a 2-year prospective RCT comparing the effects of a low-protein diet (0.8 g/kg/day) with normal

protein diet in 63 diabetic patients with a mean GFR of 80 +/- 20 mL/min and no differences in GFR were noted (Dussol et al., 2005).

Even so, Hansen et al demonstrated a better prognosis in type I diabetic patients, where either dialysis, transplantation or death occurred in 27% of the patients in the control group, as compared with only 10% of the LPD group (Hansen et al., 2002). Later in 2009, Koya's performed a prospective RCT and confirmed the lack of renoprotective effect in the longer-term prevention or delay of renal damage, in patients with type 2 diabetes (p=0.5) (Koya et al., 2009). A more recent meta-analysis confirmed that protein diet restriction slowed CKD progression in type 1 diabetic patients, but not in type 2. The estimated effect for the type 2 diabetic group was no more than roughly -0.17 mL/min/1.73 m^2 (p-value= 0.85) (Rughooputh et al., 2015).

In the most recent meta-analysis of 2023, with data from 8 clinical trials and a total of 486 patients, it was demonstrated that protein restriction had uncertain effects on renal function in diabetic patients. Still, diet compliance was not achieved in nearly half of the studies (S. Jiang et al., 2023).

The renoprotective effect of protein restriction can be reinforced proportionally with the extent of protein restriction (<0.6 g/kg/day). However, it could be argued that a decrease of more than 25% in protein intake than the one recommended in the general population on a long-term basis (given the <0.6mg/kg/day is the lowest protein requirement to avoid negative nitrogen balance) might eventually compromise metabolic balance and survival, by gradually deteriorating nutritional status. Thus, to attain proper nutritional status and avoid protein-energy wasting (PEW), nutritional supplementation with EAAs and KAs has been proposed for VLPDs (0.28g/kg/day – 0.43g/kg/day) (Ikizler et al., 2020; G. J. Ko et al., 2017). Nutritional supplementation with KAs helps maintain protein-energy status without increasing the levels of nitrogen waste products, with reduced phosphorus and acid load in VLPD, along with decreased protein degradation and enhanced protein synthesis (Koppe et al., 2019).

Over the last years, the advantages of opting for a VLPD have been backed by various studies (Brunori et al., 2007; Garneata et al., 2016; Mircescu et al., 2007; Prakash et al., 2004) and meta-analyses (Chewcharat et al., 2020; Z. Jiang et al., 2016; Palmer et al., 2017; Rhee et al., 2018; Yan et al., 2018). The most recent RCT, in 2016, demonstrated that a VLPD supplemented with KAs mitigated kidney function decline and reduced the number of patients requiring RRT by 19% ($p<0.0001$), when compared to a conventional LPD. At the end of the study, patients following a VLPD regimen noted a 3.2 mL/min lower decline in GFR per year, in comparison with the LPD group (Garneata et al., 2016).

However, unlike the majority of previous RCTs, Bellizi et al did not register any beneficial results for CKD stages 4 and 5 participants, following a supplemented VLPD with KAs. The risk of renal death did not differ from VLPD to LPD ($p=0.28$) and no difference was observed for ESRD ($p=0.51$) or mortality ($p=0.82$) (Bellizzi, Signoriello, et al., 2022).

After the 2020 KDOQI guidelines, a new systematic review and meta-analysis explored the effectiveness of restricted protein diet supplemented with KAs, when compared with a regular diet or an LPD without KAs in CKD. The authors included 17 RCTs with a total of 1459 patients and noted that complementing KAs to restricted protein diets also conserved GFR ($p=0.013$) (Chewcharat et al., 2020).

In diabetic patients, KDOQI guidelines suggest an LPD (0.6–0.8 g/kg/day) coupled with adequate energy intake, but this statement is based on opinion, and not on evidence, and it does not provide any recommendations on KA supplementation, due to a lack of evidence. Be that as it may, a 2022 systematic review evaluated the combination of a protein-restricted diet and supplemental KAs, in patients with non-dialysis DKD, and saw favorable effects on the progression of renal damage. Nevertheless, the authors highlighted several limitations, including very limited data on the initiation of dialysis and death, which prevented the authors from drawing a statistically significant conclusion (Bellizzi, Garofalo, et al., 2022).

As seen above, the latest pieces of evidence point towards a benefit of dietary protein restriction among non-diabetic CKD patients, both in LPD and in VLPD regimens, in

strong alignment with the nutritional management recommendations of the KDOQI guidelines (1A). However, the same conclusion could not be drawn for diabetic patients, which confirms that the recommendation in the guidelines is based more on opinion than on evidence.

Effect of Low Protein Diet on Nutritional Risk

CKD patients have a baseline increased risk of malnutrition due to PEW (52). PEW was defined as a state of nutritional and metabolic derangements in patients with CKD and ESRD, characterized by a simultaneous loss of systemic body protein and energy stores, ultimately leading to a loss of muscle and fat mass and cachexia (Hanna et al., 2020; Piccoli et al., 2023).

The reason why this occurs is related to the hypercatabolic status induced by uremia, malnutrition, inflammation from systemic conditions (diabetes), and auto immune conditions that generally lead to CKD and ESRD. Since malnutrition is the main risk factor for PEW, restriction of protein intake raised concerns about the possibility of aggravating PEW in CKD patients, and decreased body mass index was shown to be associated with a higher mortality of ESRD patients treated with dialysis.

Thus, investigation was made to determine whether an LPD could contribute to the risk of malnutrition.

In 2009, Cianciaruso et al presented an RCT of 423 CKD stages 4 and 5 patients, submitted to an LPD (0.55 g/kg/day) and MPD (0.8 g/kg/day) and only three participants of the LPD group (<1%) developed malnutrition, suggesting that close monitoring for nutritional status was more important to avoid malnutrition rather than the amount of protein intake itself. In contrast, 40–50% of the patients in NPD group spontaneously reduced both protein and energy intake, developing overt malnutrition at the start of dialysis and demonstrating that a free diet, in contrast to a LP one, may cause malnutrition (Cianciaruso B, Pota A, Bellizzi V, et al.,. 2009;54:1052–1061, n.d.).

The abovementioned 2016 RCT not only tested the effectiveness of VLPDs in reducing renal death, but also aimed to assess a potential increase in the risk of malnutrition. A total of 207 participants, followed up for 18 months, were divided into a VLPD with KA supplementation and an LPD, and both groups reported an average intake of 30 kcal/kg/day and preserved nutritional status (Garneata et al., 2016).

Lastly, in the most recent meta-analysis, Chewcharat et al proved that hypoproteic diets with KAs supplementation were effective in preserving GFR decline without simultaneously causing malnutrition (Chewcharat et al., 2020).

Therefore, as long as a sufficient energy intake of at least 30 kcal/kg/day is ingested, the protein intake level can be safely decreased to 0.55-0.6 g/kg/day. Moreover, a further reduction in protein intake to 0.3-0.4 g/kg/day can be achieved with the addition of KAs to ensure a sufficient balance of essential amino acids (Koppe et al., 2019), (Piccoli et al., 2023).

Limitations

One of the most significant limitations is the inadequate adherence of patients to restrictive diets, as reported in most studies.
Additionally, the definitions of protein intake are not uniform across the reported studies, which limits an accurate comparison of these studies. The small number of patients and limited follow-up periods limit the generalization of these results.

Conclusion

In conclusion, based on recent evidence, it is advisable to follow a well-designed protein-restricted diet on CKD patients between stages 3, 4 and 5, because of the favorable effects delaying the GFR decline or ESRD occurrence rates. Moreover, in older patients with advanced CKD at risk of impaired nutritional status, the prescription of an LPD diet does not seem to induce malnutrition. A concomitant adequate energy intake and lean mass maintenance is acceptable to sustain dietary management safety in these patients. Despite the positive results associated with LPDs, concerns about its feasibility persist, such as the difficulties encountered in obtaining compliance and the risk of affecting quality of life. These issues are of the utmost importance, as more in-depth information about a patient's preference for food types and a continuous effort to find new solutions for better tolerability and satisfaction are essential for a successful dietary treatment.

There are still some future questions that need to be answered, considering the natural course of CKD. Thus, further studies, such as large-scale pragmatic RCTs with larger follow-up periods, are required to better evaluate the benefits of restrictive diets.

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Anexos:

Table 1. Effect of LPDs or VLPDs on CKD progression						
Study	Study Design	Sample Size	Follow-up time	CKD stage	Intervention	Results
Teplan 2001 (Teplanl et al., n.d.)	Prospective RCT	105	36 months	3, 4	LPD (0.6 g/kg/day) + rHuEPO+ KA (I) vs. LPD+ rHuEPO (II) vs. LPD (III)	GFR decreased slightly in all groups. Group I had the lowest decline, and the difference was significant (Group I vs. Group II and III) (p<0,01)
Meloni 2002 (Meloni et al., 2002)	Prospective RCT	69 (DM)	12 months	4	LPD (0.6 g/kg/day) vs. NPD	No statistically significant differences.

Ideura 2003 (Ideura et al., 2003)	Retrospective	97	12 months	5	NPD (0.55 –1.2 kg/g/day) vs. VLPD (0.25-0.54 kg/g/day)	At 3 months : GFR slope LPD: - 0.2 mL/mon NPD: -7.1 ml/mon ($p < 0.001$) At 12 months: HD start: LPD: 42% NPD: 100%
Meloni 2004 (Meloni et al., 2004)	Prospective RCT	169	1 year	4	Non-diabetic patients: LPD (0.6 g/kg/day) vs. NPD	Non-diabetic patients: GFR slope: LPD: -3.47

					Diabetic patients: LPD (0.8 g/kg/day) vs. NPD	ml/min/1.73 m2 NPD: - 6.05 ml/min/1.73 m2 (p <0.001) Diabetic patients: No statistically significant differences.
Prakash 2004 (Prakash et al., 2004)	Prospective RCT	34	9 months	5	sVLPD (0.3 g/kg/d protein plus tablets of KAs) vs. LPD (0.6 g/kg/d protein plus placebo)	GFR difference: sVLPD: 28.1 – 27.6 ml/min/1.73m2 (p <0,72)

						LPD: 28,6 – 22,5 ml/min/1.73 m2 (p<0.015)
Levey 2006 (Levey A.S., (MDRD) Study. Am J Kidney Dis. 2006, n.d.)	Prospective RCT	585	6 years	3,4	Study A: LPD (0.6 g/Kg/day) vs. NPD	No significant benefit, slowing the development of kidney failure and the composite outcome of kidney failure and all-cause mortality.
Mircescu 2007 (Mircescu et al., 2007)	Prospective RCT	53	48 weeks	4, 5	sVLPD (0.3 g/kg/d of vegetable proteins and KAs) vs. LPD (0.6 g/kg/d)	GFR difference: sVLPD: 18.3-15.4 ml/min/ 1.73 m2 LPD: 17.9 – 13.4 ml/min/ 1,3 m2

						RRT initiation: sVLPD: 4% LPD: 27%
Brunori 2007 (Brunori et al., 2007)	Prospective RCT	112	26,5 months	5	sVLPD vs. Dialysis	Postponing dialysis treatment by a median of 10.7 months.
Eyre 2008 (Eyre et al., 2008)	Retrospective	122	6 months	4, 5	LPD (0,6 g/kg/day) vs. NPD	GFR slope during the 6 months before dialysis: LPD: -4.1 mL/min/ year NPD: -13.4 mL/min/year (p<0,001)

Menon 2009 (Menon V., (MDRD) Study. Am J Kidney Dis. 2009;53:208–217, n.d.)	Prospective RCT	255	3,2 years	4, 5	Study B: sVLPD (0.28 g/kg/day) vs. LPD (0.58 g/kg/day)	No statistically significant differences on eGFR or dialysis start of sVLPD but appeared to increase the risk of death.
Cianciarusso 2009 (Cianciaruso B, Pota A, Bellizzi V, et al.. 2009;54:1052–1061, n.d.)	RCT	423	32 months	4,5	LPD (0.55 g/kg/day) vs. MPD (0.80 g/kg/day)	No statistically significant differences on eGFR or dialysis start.

Garneata 2016 (Garneata et al., 2016)	RCT	207	18 months	4,5	sVLPD (0.3 g/kg/ day of vegetable proteins) vs. LPD (0.6 g/kg/ day)	GFR difference: LPD: 18.0 - 15.1 ml/min sVLPD: 17.9 - 10.8 ml/min RRT initiation: sVLPD: 11% LPD: 30% Mean time to RRT initiation: sVLPD: 38 weeks LPD: 23 weeks ($p<0.0001$)

Satirapoj 2018 (Satirapoj et al., 2018)	Retrospective	140	12 months	3, 4	LPD (0.6 g/kg/day) vs. sVLPD (0.3 g /kg/day plus KA/EAA of 100 mg/kg/day)	GFR slope: LPD: −5.2 mL/min/1.73 m2 sVLPD: −0.3 mL/min/1.73 m2 (p<0.001)
Baragetti 2020 (Baragetti et al., 2020)	Retrospective	299	30 months (median) 11.2–113.8 months (range)	4	CPD (0.8 g/kg/day) vs. LPD (0.6 g/kg/day) vs. NPD	GFR difference: NPD: - 6.0 mL/min/1.73 m2 LPD: -2.9 mL/min/1.73 m2 CPD: +0.36 ml/min/1.73 m2 RRT initiation: (70 months) NPD: 57,6%,

						LPD: 35,6% CPD: 25,6% ($p < 0.001$). Postponing dialysis 21 and 24 months later in CPD and LPD groups compared with the NPD patients. ($p <0,001$ and $p=0,003$, respectively)
Bellizzi 2022 (Bellizzi et al., 2022)	RCT	223	36 months	4,5	sVLPD (0.35 g/kg/day) vs. LPD (0.60 g/kg/ day)	No significant differences in GFR slope

						sVLPD: –1.08 mL/min/1.73m2 LPD: GFR slope –0.96 mL/min/1.73m2 No difference was observed for ESRD occurence.
Otani 2023 (Otani et al., 2023)	Retrospective	325	4,1 years	4, 5	Group 1: < 0.5 g/kg/day vs. Group 2: 0.5 ≤ PI < 0.6 g/kg/day vs. Group 3: 0.6 ≤ PI < 0.8 g/kg/day vs. Group 4: ≥ 0.8 g/kg/day	LPD therapy of 0.5 g/kg/day or less was significantly related to a lower risk of RRT and all-cause mortality. (p=0.042)
CPD: Controlled Protein diet; eGFR: Glomerular Filtration Rate; KA: Keto-acids, LPD: Low-protein diet; PI: Protein intake; RCT: Randomized Clinical Trial; rHuEPO: Recombinant Human Erythropoietin; RRT: Renal replacement theraphy; s: Supplementation; VLPD: Very low-protein diet						