Very low protein diet supplemented with keto analogues compared to low protein diet in pre-dialysis chronic kidney disease patients

Cristóbal Walbaum[1,2], Rodrigo Sepúlveda[1,2,3*]

[1] *Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*
[2] *Proyecto Epistemonikos, Santiago, Chile*
[3] *Departamento de Nefrología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*

*** Corresponding author** rrsepulveda@uc.cl

Citation Walbaum C., Sepúlveda R. Very low protein diet supplemented with keto analogues compared to low protein diet in pre-dialysis chronic kidney disease patients. *Medwave* 2022;22(05):e8697

Doi 10.5867/medwave.2022.05.8697

Submission date 04/10/2019
Acceptance date 17/08/2020
Publication date 24/06/2022

Origin This article is a product of the Evidence Synthesis Project of Epistemonikos Fundation, in collaboration with Medwave for its publication.

Type of review Not non-blind peers by the UC Evidence Center methodological team in collaboration with Epistemonikos Evidence Synthesis Project.

Potential conflicts of interest The authors do not have relevant interests to declare.

Key words ketoanalogue, low protein diet, chronic kidney disease, Epistemonikos, GRADE.

Abstract

Introduction

It has been proposed that a very low protein diet supplemented with keto analogues in pre-dialysis chronic kidney disease patients can slow the progression to a terminal disease and delay the start of renal replacement therapy, without a malnutrition risk. However, its common use has not yet been implemented due to the uncertainty of its efficacy and safety.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified eight systematic reviews including 14 studies overall, of which 12 were randomized trials. We concluded that a very low protein diet supplemented with keto analogues delays the progression to end-stage kidney disease, probably reduces the fall or deterioration of renal function, could reduce mortality by any cause y result in little or no difference in malnutrition risk, but the certainty of the evidence is low for these last two results.

Problem

Chronic kidney disease is defined as the presence of renal injury or glomerular filtration rate <60 mL/min/1,73m^2 for at least three months independent of the cause [1]. Chronic kidney disease is a worldwide public health problem, due to its high and increasing prevalence, elevated costs and poor prognosis. The most important complications are acute renal failure, end-stage kidney disease, cardiovascular disease and increased mortality.

Due to the high impact chronic kidney disease has, strategies have been looked for to slow down the progression and ameliorate the symptoms. Because protein related by-products accumulate in chronic kidney disease (nitrogen products, acids, phosphorus, among

others), and moreover, an excess of proteins generates renal parenchymal damage; a protein restricted diet has been proposed as a therapeutic measure [2].

In fact, a low protein diet of 0.6-0.8 g/kg/day could be beneficial in avoiding progression to end-stage kidney disease [3]. It has been stated that an even higher protein restriction (0.3 g/kg/day) can increase the benefit as long as the correct calorie intake is kept [4]. This may be achieved by a keto analogue supplementation, which are nutrients similar to amino acids, but free of the nitrogen branch. It has been proposed that a very low protein diet supplemented with keto analogues may reduce nitrogen ingestion, increase calorie intake and avoid excess protein deleterious effects in chronic kidney disease.

Key messages

- Very low protein diet supplemented with keto analogues in pre-dialysis slightly delays the progression to end-stage kidney disease.
- Very low protein diet supplemented with keto analogues may reduce mortality by any cause (low certainty evidence).
- Very low protein diet supplemented with keto analogues probably reduces the fall or deterioration of renal function.
- Very low protein diet supplemented with keto analogues could result in little or no difference in the risk of malnutrition (low certainty evidence).

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified eight systematic reviews [5], [6], [7], [8], [9], [10], [11], [12], including 14 primary studies reported in 29 references [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41] of which 12 are randomized trials reported in 26 references [14], [15], [17], [18], [19], [20], [21], [22], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41]. Three of the identified randomized trials [17], [20], [28] also reported the results of trials that did not assess the use of keto analogs. Although these are reflected in the evidence matrix, they were not included in this summary. The table and summary in general are based on the 12 randomized trials [14], [15], [17], [19], [20], [28], [30], [31], [33], [35], [36], [37], as the observational studies did not increase the level of certainty of the evidence, nor added any additional relevant information.
What types of patients were included*	All trials were made in adult patients with chronic kidney disease in pre-dialysis stage. Eleven trials describe the chronic kidney disease stage of the patients [14], [15], [17], [19], [20], [28], [30], [31], [33], [35], [37]. Ten included patients with glomerular filtration rate of 30 ml/min/1.73m^2 or less [14], [15], [17], [19], [20], [28], [30], [31], [33], [37] and one trial included patients with creatinine clearance between 20 and 50 ml/min/1,73m2 [35]. One trial does not describe the chronic kidney disease stage of the patients [36]. Ten trials excluded patients with comorbidities such as cancer, systemic diseases, poorly controlled hypertension or

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	insulin-requiring diabetes mellitus [14], [15], [19], [20], [28], [31], [33], [35], [36], [37].
What types of interventions were included*	All trials evaluated a very low protein diet (0.3 gr/kg/day) supplemented with keto analogues with or without essential amino acids. All trials compared against a low protein diet (0.6 g/kg/day). Only one trial added a placebo in the control group [35] and only one trial added a calcium supplement to the control group [30].
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows: • Mortality: all cause death, renal death • End stage kidney disease progression • End or change in glomerular filtration rate • Protein energy wasted • Blood levels of: blood urea nitrogen, albumin, creatinine, calcium, phosphorus, parathormone, cholesterol, triglycerides, haemoglobin • Nutritional parameters such as: body mass index, final weight, lean mass, arm muscle circumference • Others: proteinuria, systolic blood pressure, diastolic blood pressure. The average follow up of the trials was 17 months, with a range between 2 to 50 months.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of findings

The information about the effects of a very low protein diet supplemented keto analogues is based on 12 randomized trials which included 1064 patients.

Five trials measured the outcome death by any cause (584 patients) [14], [20], [28], [31], [33]; eight trials measured the outcome end stage kidney disease progression (849 patients) [14], [15], [17], [20], [28], [31], [33], [37]; four trials measured the outcome fall or deterioration of renal function (535 patients) [15], [20], [28], [33]; seven trials measured the outcome malnutrition (477 patients) [15], [19], [20], [28], [31], [33], [35]. No systematic review analysed the outcomes hospitalizations and cardiovascular death.

The summary of findings is the following:

- The use of very low protein diet supplemented keto analogues compared to low protein diet in pre dialysis patients may reduce mortality by any cause (low certainty evidence).
- The use of very low protein diet supplemented keto analogues compared to low protein diet in pre dialysis patients reduces the progression to end-stage kidney disease.
- The use of very low protein diet supplemented keto analogues compared to low protein diet in pre dialysis patients probably reduces the fall or deterioration of renal function.
- The use of very low protein diet supplemented keto analogues compared to low protein diet in pre dialysis patients may make little or no difference in malnutrition (low certainty evidence).
- No evidence was found that looked at cardiovascular death.
- No evidence was found that looked at hospitalizations.

Very low protein diet supplemented with keto analogues in pre dialysis patients

Patients Adults in pre dialysis chronic kidney disease
Intervention Very low protein diet supplemented with keto analogues (VLPD+KA)
Comparison Low protein diet (LPD)

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITH LPD	**WITH VLPD + KA**		
	Difference: patients per 1000			
Death by any cause	192 per 1000	163 per 1000	RR 0.85 (0.43 to 1,70)	⊕⊕◯◯[1,2] Low
	Difference: 29 less patients (Margin of error: 109 less to 134 more)			
Progression to end-stage kidney disease	647	460	RR 0.71 (0.54 to 0.93)	⊕⊕⊕⊕ High
	Difference: 187 less patients (Margin of error: 45 to 298 less)			
Fall or deterioration of renal function**	The annual fall or deterioration of renal function was in average 0.32 standard deviations higher in the very low protein diet with keto analogues group.		--	⊕⊕⊕◯[3] Moderate
	SMD***: 0.32 (Margin of error: 0.15 less to 0.49 less)			
Malnutrition****	4.0 g/dL	4.1 g/dL	--	⊕⊕◯◯[2, 3] Low
	MD: 0.09 g/dL (Margin of error: 0.03 worse to 0.21 better)			
Cardiovascular death	The outcome cardiovascular death was not measured or reported by any systematic review		--	--
Hospitalizations	The outcome hospitalizations was not measured or reported by any systematic review		--	--

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
SMD: Standard mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITH LPD** is based on the risk in the control group of the trials. The risk **WITH VLPD+KA** (and its margin of error) is calculated from relative effect (and its margin of error).
** Fall or deterioration of renal function was measured through different methods of glomerular filtration rate in those studies which had a follow up of 48 weeks or more.
***Standard mean difference is used when the outcome has been measured in different scales and it is hard to interpret clinically. A general rule is that values near 0.2 have little clinical relevance, values of 0.5 have moderate relevance and values over 0.8 have an important clinical relevance.
****Malnutrition was measured from albumin serum levels, where lower levels indicate a higher malnutrition risk. This parameter was chosen because no other measured parameter was considered better correlated to the outcome chosen.

[1] The certainty of evidence was downgraded one level due to inconsistency of results between the trials (i^2=75%).
[2] The certainty of evidence was downgraded one level due to imprecision, as both ends of the confidence interval generate different decisions.
[3] The certainty of evidence was downgraded two levels due to imprecision as the fall or deterioration of renal function evaluated with the glomerular filtration rate was estimated as creatinine clearance or plasmatic creatinine (parameter altered by nutritional status). Thus, there may be differences between groups without an expressed result. The result malnutrition was measured as albumin serum levels, which is an indirect nutritional parameter.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

These results apply to adult patients capable of following a strict diet, with chronic kidney disease in pre dialysis stage, with a glomerular filtration rate ≤30 mL/min/,.73m^2.

These results may be applied to chronic kidney disease patients and estimated glomerular filtration rate >30 mL/min/1,73m^2, but there are no studies that confirm its utility in these patients.

These results do not apply in patients with important comorbidities, such as systemic diseases, badly controlled hypertension and insulin-requiring diabetes.

About the outcomes included in this summary

The outcomes included in the summary of findings table are, according to the authors, those clinically relevant for decision making. This generally matches with what was reported by the systemic reviews, except for hospitalizations and cardiovascular death, which were not reported by any review.

As the outcome malnutrition was not measured directly, serum albumin level was used as an indirect parameter to estimate nutritional state because there is a correlation between serum albumin levels and mortality in chronic kidney disease [42].

Balance between benefits and risks, and certainty of the evidence

The benefits of a very low protein diet with ketoanalogues include the reduction in progression to end-stage chronic kidney disease (high certainty of evidence) and its use could reduce death by any cause, even though this result has a low certainty of evidence.

On the other hand, very low protein diet with ketoanalogues compared to low protein diet in chronic kidney disease in pre dialysis stage could result in little or no difference in malnutrition and probably reduces the fall or deterioration of glomerular filtration rate.

Considering the observed effects, the risk/benefit balance probably favours the use of a very low protein diet with ketoanalogues over a low protein diet alone.

Resource considerations

No systematic review identified made an analysis on the differences in costs between the interventions. Nonetheless, a very low protein diet with ketoanalogues represents an additional cost for the patient as it includes a new drug and extra nutritional and medical evaluations.

What would patients and their doctors think about this intervention

Patients which manage to pay for this intervencion are, in general, happy with it, as it is relatively simple and it gives them a chance to delay renal replacement therapy and its repercussions.

The experience for their doctors has been positive, managing a good therapy adherence from their patients to the treatment. The main problem they see is the price of this therapy, as it must be paid by the patients.

Differences between this summary and other sources

The conclusions of this summary are consistent with all included systematic reviews [2], [7], [17] which consider that there is a benefit of stepwise removal on the outcomes of pulp exposure, restoration failure and signs of pulp pathology. However, there is uncertainty given that the level of confidence of the evidence is low.

From clinical practice guidelines consulted [14], [15], [16], only the Ministry of Health of Chile guideline [16] mentions the two-step technique (stepwise) for the management of caries lesions in permanent teeth, and temporary vital and asymptomatic caries lesions that require operative treatment. It is recommended to perform partial caries removal therapies in one or two stages.

Could this evidence change in the future?

The outcomes death by any cause and malnutrition may change as new trials appear, as their certainty of evidence was low.

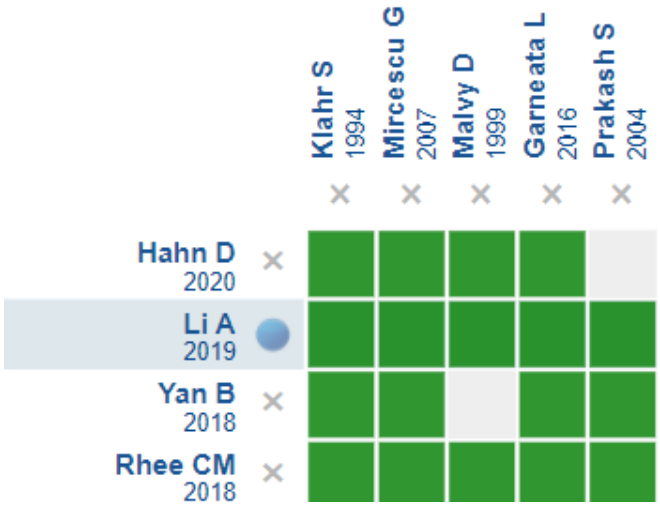
The outcome fall or deterioration of filtration rate may not change as new trials appear, as its certainty of evidence is moderate.

It is unlikely that the outcome progression to end-stage kidney disease changes as its results have a high level of certainty and consistency.

We found one systematic review in progress in PROSPERO [46] and three ongoing randomized controlled trials in International Clinical Trials Registry Platform [47], [48], [49], results which have not yet been published, which can contribute with new findings to the outcomes measured.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the interactive version: Keto Analogues and Very Low Protein Diet in Pre Dialysis Chronic Kidney Disease

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

Referencias

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [Internet]. Kdigo.org. 2013. Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
2. Mitch WE. Dietary protein restriction in chronic renal failure: nutritional efficacy, compliance, and progression of renal insufficiency. J Am Soc Nephrol. 1991 Oct;2(4):823-31.
3. Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care. 2017 Jan;20(1):77-85.
4. Di Micco L, Di Lullo L, Bellasi A, Di Iorio BR. Very Low Protein Diet for Patients with Chronic Kidney Disease: Recent Insights. J Clin Med. 2019;8(5):718.
5. Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. Cochrane Database Syst Rev. 2020 Oct 29;10:CD001892. doi: 10.1002/14651858.CD001892.pub5. PMID: 33118160.
6. Zarazaga A, García-De-Lorenzo L, García-Luna PP, García-Peris P, López-Martínez J, Lorenzo V, Quecedo L, Del Llano J. Nutritional support in chronic renal failure: systematic review. Clin Nutr. 2001 Aug;20(4):291-9. Review. PubMed PMID: 11478825.
7. Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. J Cachexia Sarcopenia Muscle. 2018 Apr;9(2):235-245. doi: 10.1002/jcsm.12264.

Epub 2017 Nov 2. PubMed PMID: 29094800; PubMed Central PMCID: PMC5879959.

8. Li A, Lee HY, Lin YC. The Effect of Ketoanalogues on Chronic Kidney Disease Deterioration: A Meta-Analysis. Nutrients. 2019 Apr 26;11(5). pii: E957. doi: 10.3390/nu11050957. PubMed PMID: 31035482; PubMed Central PMCID: PMC6566830.
9. Jiang Z, Zhang X, Yang L, Li Z, Qin W. Effect of restricted protein diet supplemented with keto analogues in chronic kidney disease: a systematic review and meta-analysis. Int Urol Nephrol. 2016 Mar;48(3):409-18. doi: 10.1007/s11255-015-1170-2. Epub 2015 Nov 30. Review. PubMed PMID: 26620578.
10. Fouque D, Wang P, Laville M, Boissel JP. Low protein diets delay end-stage renal disease in non-diabetic adults with chronic renal failure. Nephrol Dial Transplant. 2000 Dec;15(12):1986-92. PubMed PMID: 11096144.
11. Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. BMJ. 1992 Jan 25;304(6821):216-20. PubMed PMID: 1531426; PubMed Central PMCID: PMC1881445.
12. Yan B, Su X, Xu B, Qiao X, Wang L. Effect of diet protein restriction on progression of chronic kidney disease: A systematic review and meta-analysis. PLoS One. 2018 Nov 7;13(11):e0206134. doi: 10.1371/journal.pone.0206134. eCollection 2018. PubMed PMID: 30403710; PubMed Central PMCID: PMC6221301.
13. Bellizzi V, Di Iorio BR, De Nicola L, Minutolo R, Zamboli P, Trucillo P, Catapano F, Cristofano C, Scalfi L, Conte G; ERIKA Study-group. Very low protein diet supplemented with ketoanalogs improves blood pressure control in chronic kidney disease. Kidney Int. 2007 Feb;71(3):245-51. Epub 2006 Oct 11. PubMed PMID: 17035939.
14. Chauveau P, Lebkiri B, Ployard F, Ciancioni C, Man NK, Jungers P. [Effect of keto analogs of essential amino acids on the progress of advanced chronic renal insufficiency: controlled prospective study]. Nephrologie. 1986;7(4):137-42. French. PubMed PMID: 3796783.
15. Di Iorio BR, Minutolo R, De Nicola L, Bellizzi V, Catapano F, Iodice C, Rubino R, Conte G. Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure. Kidney Int. 2003 Nov;64(5):1822-8. PubMed PMID: 14531817.
16. Di Iorio BR, Bellizzi V, Minutolo R, De Nicola L, Iodice C, Conte G. Supplemented very low-protein diet in advanced CRF: is it money saving? Kidney Int. 2004 Feb;65(2):742. PubMed PMID: 14717953.
17. European Study Group for the Conservative Management of Chronic Renal Failure. Dietary compliance in the trial of the European Study Group. A preliminary analysis. European Study Group for the Conservative Management of Chronic Renal Failure. Contributions to Nephrology 1990; 81:61–70. MEDLINE: 2093513
18. European Study Group for the Conservative Management of Chronic Renal Failure. Dietary compliance in the trial of the European Study Group. An interim analysis. European Study Group for the Conservative Management of Chronic Renal Failure. Contributions to Nephrology 1992;98:133–41. MEDLINE: 1493725
19. Feiten SF, Draibe SA, Watanabe R, Duenhas MR, Baxmann AC, Nerbass FB, Cuppari L. Short-term effects of a very-low-protein diet supplemented with ketoacids in nondialyzed chronic kidney disease patients. Eur J Clin Nutr. 2005 Jan;59(1):129-36. PubMed PMID: 15354199.
20. Garneata L, Mircescu G. Effect of low-protein diet supplemented with keto acids on progression of chronic kidney disease. Journal of Renal Nutrition 2013;23(3): 210–3. MEDLINE: 23611549
21. Garneata L, Stancu A, Dragomir D, Mircescu G. Effect of very low protein diet supplemented with ketoanalogues of the essential amino acids on the progression of chronic kidney disease [abstract]. Nephrology Dialysis Transplantation 2014;29(Suppl 3):iii39. EMBASE: 71491557]
22. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. Journal of the American Society of Nephrology 2016;27(7):2164–76. MEDLINE: 26823552
23. Gin H, Aparicio M, Potaux L, Merville P, Combe C, de Precigout V, Bouchet JL, Aubertin J. Low-protein, low-phosphorus diet and tissue insulin sensitivity in insulin-dependent diabetic patients with chronic renal failure. Nephron. 1991;57(4):411-5. PubMed PMID: 2046822.
24. Jungers P, Chauveau P, Ployard F, Lebkiri B, Ciancioni C, Man NK. Comparison of ketoacids and low protein diet on advanced chronic renal failure progression. Kidney International - Supplement 1987;22:S67–71. MEDLINE: 3323621
25. Klahr S. Role of dietary protein and blood pressure in the progression of renal disease. Kidney Int. 1996 Jun;49(6):1783-6. Review. PubMed PMID: 8743497.
26. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. 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. PubMed PMID: 8114857.
27. Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, Steinman TI, Wang SR, Yamamoto ME. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol. 1995 Jun;5(12):2037-47. Erratum in: J Am Soc Nephrol 1995 Oct;6(4):1318. PubMed PMID: 7579052.
28. Levey AS, Adler S, Caggiula AW, England BK, Greene T, Hunsicker LG, Kusek JW, Rogers NL, Teschan PE. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. Am J Kidney Dis. 1996 May;27(5):652-63. PubMed PMID: 8629624.
29. Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. J Am Soc Nephrol. 1999 Nov;10(11):2426-39. Review. PubMed PMID: 10541304.
30. Lindenau K, Abendroth K, Kokot F, Vetter K, Rehse C, Fröhling PT. Therapeutic effect of keto acids on renal osteodystrophy. A prospective controlled study. Nephron. 1990;55(2):133-5. PubMed PMID: 2132299.
31. Malvy D, Maingourd C, Pengloan J, Bagros P, Nivet H. Effects of severe protein restriction with ketoanalogues in advanced renal failure. J Am Coll Nutr. 1999 Oct;18(5):481-6. PubMed PMID: 10511331.
32. Menon V, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW, Greene T, Levey AS, Sarnak MJ. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. Am J Kidney Dis. 2009 Feb;53(2):208-17. doi: 10.1053/j.ajkd.2008.08.009. Epub 2008 Oct 31. PubMed PMID: 18950911.
33. Mircescu G, Gârneaţă L, Stancu SH, Căpuşă C. Effects of a supplemented hypoproteic diet in chronic kidney disease. J Ren Nutr. 2007 May;17(3):179-88. PubMed PMID: 17462550.
34. Nivet H, Maingourd C, Malvy D, Pengloan J, Bagros PH. Effects of severe protein-restriction with ketoanalogues in advanced renal failure [abstract]. Journal of the American Society of Nephrology 1992;3(3):286.
35. Prakash S, Pande DP, Sharma S, Sharma D, Bal CS, Kulkarni H. Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. J Ren Nutr. 2004 Apr;14(2):89-96. PubMed PMID: 15060873.
36. Teplan V, Schuck O, Bubenicek P, Mengerova O, Tesarova Z, Hajny J, et al. The effect of long-term administration of a low-protein diet on the metabolic status and progression of chronic renal failure: a multicentre study [abstract]. Nephrology Dialysis Transplantation 1998;13: 820. CENTRAL: CN–00301551].
37. Teschan PE, Beck GJ, Dwyer JT, Greene T, Klahr S, Levy AS, Mitch WE, Snetselaar LG, Steinman TI, Walser M. Effect of a

ketoacid-aminoacid-supplemented very low protein diet on the progression of advanced renal disease: a reanalysis of the MDRD feasibility study. Clin Nephrol. 1998 Nov;50(5):273-83. PubMed PMID: 9840314.

38. Rebholz CM, Zheng Z, Grams ME, Appel LJ, Sarnak MJ, Inker LA, Levey AS, Coresh J. Serum metabolites associated with dietary protein intake: results from the Modification of Diet in Renal Disease (MDRD) randomized clinical trial. Am J Clin Nutr. 2019 Mar 1;109(3):517-525. doi: 10.1093/ajcn/nqy202. PMID: 30753252; PMCID: PMC6408209.
39. Grams ME, Tighiouart H, Coresh J, Sarnak MJ. Vascular disease-associated mortality during CKD progression: the MDRD study [abstract no: TH-PO332]. Journal of the American Society of Nephrology. 2011;22(Abstract Suppl):189A.
40. Garneata, L., Stancu, A., Dragomir, D., Stefan, G., Mircescu, G.. Vegetarian very low protein diet supplemented with ketoanalogues in stage 5 ckd patients. Nephrology Dialysis Transplantation. 2018;33((Garneata L.; Stefan G.; Mircescu G.) Department of Nephrology and Internal Medicine, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania):i472.
41. Garneata, L., Mocanu, E.-A., Stancu, A., Dragomir, D., Stefan, G., Mircescu, G.. Vegetarian very low protein diet supplemented with ketoanalogues-effects on mineral bone metabolism disorders in advanced chronic kidney disease. Nephrology Dialysis Transplantation. 2018;33((Garneata L.; Stefan G.; Mircescu G.) Department of Nephrology and Internal Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania):i167-i168.
42. Keane WF, Zhang Z, Lyle PA, Cooper ME, de Zeeuw D, Grunfeld JP, Lash JP, McGill JB, Mitch WE, Remuzzi G, Shahinfar S, Snapinn SM, Toto R, Brenner BM; RENAAL Study Investigators. Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL study. Clin J Am Soc Nephrol. 2006 Jul;1(4):761-7. Epub 2006 May 17. PubMed PMID: 17699284.
43. Chronic Kidney Disease; CKD: Major Recommendations (2010) [Internet]. Andeal.org. 2010 [cited 5 July 2019]. Available from: https://www.andeal.org/vault/pq95.pdf
44. NKF KDOQI Guidelines [Internet]. Kidneyfoundation.cachefly.net. 2000 [cited 5 July 2019]. Available from: http://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_nutrition/doqi_nut.html
45. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [Internet]. Kdigo.org. 2012 [cited 5 July 2019]. Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
46. Xin Zhang, Bin Fu, Meijuan Yang, Tongyan Zhang. Effect of protein-restricted diet supplemented with keto acids or essential amino acids on progression of non-dialysis chronic kidney disease: systematic review and meta-analysis of randomised controlled trials. PROSPERO 2018 CRD42018020421 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018020421
47. Paniagua J. Ketoanalogues and Stage 4 CKD - Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. [cited 5 July 2019]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03818568
48. Mircescu G. Supplemented Very Low Protein Diet and the Progression of Chronic Kidney Disease - Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. [cited 5 July 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02031224
49. Li X. Effects of Low Protein Diet Supplemented Keto-/Amino Acid in Preventing the Progression of Chronic Kidney Disease (CKD)- ELPD Study - Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. [cited 5 July 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT01418508

Correspondence to
Centro Evidencia UC
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago
Chile