23rd Asian Pacific Congress of Nephrology, Noon Sympoisun 2025-12-07

Potential Synergies of Ptien Reduction and Drug Treatment in CKD Patients with and without Diabetes: The Role of Keto-Analogues

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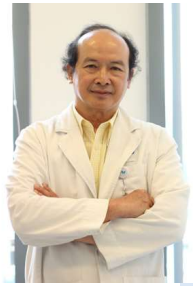
Associate Editor, **Clinical Nutrition** (ESPEN flagship)
Editor at large, **Clin J Am Soc Nephrol** (CJASN)



Kính mời quý đồng nghiệp đến tham dự

ANNUAL CONGRESS OF THE HCMC SOCIETY OF DIALYSIS THERAPIES

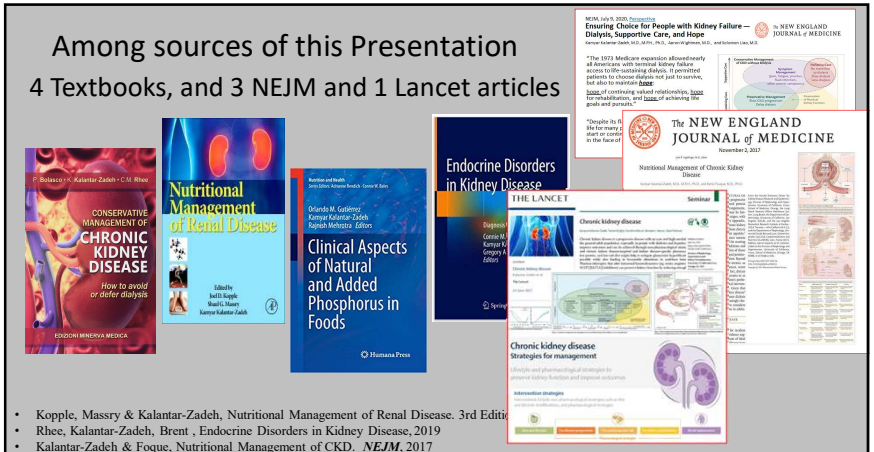
Disclosure of Financial Relationships

Kamyar Kalantar-Zadeh, MD, MPH, PhD

Relevant to this presentation:
Dr. K. Kalantar-Zadeh has received honoraria from Fresenius (Kabi).
USA National Institutes of Health (NIH)
US Veterans Affairs (VA)

Among sources of this Presentation

4 Textbooks, and 3 NEJM and 1 Lancet articles



- Kopple, Massry & Kalantar-Zadeh, Nutritional Management of Renal Disease. 3rd Editi
- Rhee, Kalantar-Zadeh, Brent , Endocrine Disorders in Kidney Disease, 2019
- Kalantar-Zadeh & Foque, Nutritional Management of CKD. ***NEJM***, 2017
- Kalantar-Zadeh, Wightman, Lia. Ensuring Choice for CKD, Dialysis, Supportive Care & Hope. ***NEJM***, 2020
- Kalantar-Zadeh et al, The ***Lancet*** 2021

What are the indications for keto-analogues use?

LPD: Low protein Diet, VLDP: Very low Protein Diet

1. LPD in CKD patients (at any stage) with (or at risk of) **Malnutrition** or **Protein-Energy Wasting** (PEW)
2. VLPD in **advanced CKD** GFR <25% (very low kidney function, VLKF) *[currently the main indication of the Fresenius Kabi product]*
3. LPD in **CKD 3-5** <50% (Low Kidney Function, LKF) or transplanted patients with LKF
4. LPD at any CKD stage but with **"heavy" proteinuria** >1g/g
5. LPD in HD and PD patients (ESRD) with **residual renal function** (RRF) for **incremental dialysis** to prolong RRF and lower dialysis dose/frequency
6. Vegan Diet (VLPD or LPD), making vegan diet safer for CKD [and for non-CKD but with **muscle-building** puposes?]
7. **Liver disease** with hyperammonemia states: cirrhosis, urea cycle defects, (not nephrology)

Combing pharmacotherapy and Keto-acid supplemented diet

KDOQI
KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE
National Kidney Foundation
KDOQI CLINICAL

eat right. Academy of Nutrition and Dietetics

REVIEW ARTICLE

The International Society of Renal Nutrition and Metabolism Commentary on the National Kidney Foundation and Academy of Nutrition and Dietetics KDOQI Clinical Practice Guideline for Nutrition in Chronic Kidney Disease

Brandon M. Kistler, PhD, RD,* Linda W. Moore, PhD, RDN,† Debbie Benner, MS, RD, CSR,‡ Annabel Biruete, PhD, RD,§ Mona Boaz, RD, PhD,¶ Giuliano Brunori, MD,** Jing Chen, MD, PhD,†† Christiane Drechsler, MD,‡‡ Fitsum Guebre-Egziabher, MD, PhD,§§ Mary Kay Hensley, MS, RDN,¶¶ Kunitoshi Iseki, MD,*** Csaba P. Kovesdy, MD,††† Martin K. Kuhlmann, MD,‡‡‡ Anita Saxena, MD, PhD,§§§ Pieter ter Wee, MD, PhD,¶¶¶ Amanda Brown-Tortorici, MS, RD, CSCS,**** Giacomo Garibotto, MD,†††† S. Russ Price, PhD,‡‡‡‡ Angela Yee-Moon Wang, MD, PhD,§§§§ and Kamyar Kalantar-Zadeh, MD, MPH, PhD****

KDOQI Clinical Practice Guidelines for Nutrition in Chronic Kidney Disease: 2020 Update, ***AJKD*** 2020.
ISRNM Commentary on the NKF and AND KDOQI Clinical Practice Guideline for Nutrition in CKD, ***JReN*** 2020.

The NKF KDOQI Guidelines (2020)

Guideline 3.0: Statements on Protein Amount

Protein Restriction, Non-Dialysis & Without Diabetes

3.0.1 In adults with **CKD 3-5 who are metabolically stable**, we recommend under close clinical supervision, protein restriction with or without keto acid analogs, to reduce risk for ESRD/death (1A) and improve QoL (2C).

- A low protein diet providing **0.55 to 0.60 g dietary protein/kg body weight/day**, OR
- A very-low protein diet providing 0.28 to 0.43 g dietary protein/kg body weight/day with additional keto acid analogs to meet protein requirements (0.55 to 0.60 g /kg body weight/day)

Dietary Protein Intake, Non-Dialysis & With Diabetes

3.0.2 In the adult with **CKD 3-5 and who has diabetes**, it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of **0.6 to 0.8 g /kg body weight per day** to maintain a stable nutritional status and optimize glycemic control (OPINION).

KDOQI Clinical Practice Guidelines for Nutrition in Chronic Kidney Disease: 2020 Update. ***AJKD*** 2020.
ISRNM Commentary on the NKF and AND KDOQI Clinical Practice Guideline for Nutrition in CKD. ***JReN*** 2020.

The KDIGO CKD Guidelines (2024)

Practice Point 3.3.1: Advise people with CKD to adopt healthy and diverse diets with a higher consumption of plant-based foods compared to animal-based foods and a lower consumption of ultraprocessed foods.
Practice Point 3.3.2: Use renal dietitians or accredited nutrition providers to educate people with CKD about dietary adaptations regarding sodium, phosphorus, potassium, and protein intake, tailored to their individual needs, and severity of CKD and other comorbid conditions.

Recommendation 3.3.1.1: We suggest maintaining a protein intake of 0.8 g/kg body weight/d in adults with CKD G3–G5 (2C).
Practice Point 3.3.1.1: Avoid high protein intake (>1.3 g/kg body weight/d) in adults with CKD at risk of progression.
Practice Point 3.3.1.2: In adults with CKD who are willing and able, and who are at risk of kidney failure, consider prescribing, under close supervision, a very low–protein diet (0.3–0.4 g/kg body weight/d) supplemented with essential amino acids or ketoacid analogs (up to 0.6 g/kg body weight/d).
Practice Point 3.3.1.3: Do not prescribe low- or very low–protein diets in metabolically unstable people with CKD.

KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD, ***KI***, 2024.

KDOQI and ISRNM Dietary Protein Intake suggested targets

REVIEW ARTICLE

The Internation
and Metabolisn
National Kidne
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Practice Guidel
Kidney Disease

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Angela Yee-Moon Wang, MD

Table 1. Ranges of dietary protein intake vis-à-vis relevant kidney disease conditions in the context of the KDOQI CPG in Kidney Disease 2020

Dietary Protein Intake Range	Daily Grams of Protein Intake per kg Body Weight (g/kg/day)*	Comment
Protein-free diet	<0.25 g/kg/day	Generally not recommended for any person including CKD patients.
Very low-protein diet	0.25–0.55 g/kg/day	Usually supplemented with essential amino acids or their ketoacids or hydroxy-acids. KDOQI CPG recommends 0.28 to 0.43 g/kg/day with additional keto acid/amino acid analogs to meet protein requirements (0.55 to 0.60 g/kg body weight/day) for metabolically stable CKD patients without diabetes.
Low-protein diet for nondiabetic CKD‡	0.55–0.8	Recommended by KDOQI CPG for CKD patients without diabetes.
Low-protein diet (for DKD‡)	0.6–0.8 g/kg/day	More consistently recommended for advanced CKD (eGFR <45 ml/min/1.73m^2 or substantial proteinuria), usually no supplementation is needed as long as the regimen contains at least 50% high biologic value proteins. This range is recommended by KDOQI CPG for CKD patients with diabetes.
Moderately low-protein intake	0.8–1.0 g/kg/day	Recommended range for adults without CKD but at high risk of CKD including those with a solitary kidney (following nephrectomy), diabetes mellitus, hypertension, and polycystic kidneys.
Moderate protein intake	1.0–1.2 g/kg/day	Recommended by KDOQI CPG for metabolically stable patients on maintenance HD or PD.
Moderately high-protein diet	1.2–1.5 g/kg/day	Reported protein intake of average United States adult without CKD.
High- to very high–protein diet	>1.5 g/kg/day	Can be used over limited period of time for acute conditions such as hypercatabolic AKI, high-grade burns, and PEW.

Very Low Protein Diet (with supplements → keto-analogues)

0.6-0.8 g/kg/day (PLADO) >50% Plant Protein

AKI, acute kidney injury; CKD, chronic kidney disease; CPG, clinical practice guideline; DKD, diabetic kidney disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HD, hemodialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; PD, peritoneal dialysis; PEW, protein-energy wasting.

Adapted from Supplementary-Appendix Table S3 by Kalantar-Zadeh and Fouque.[1]

*KDOQI CPG in Kidney Disease 2020 states it may be reasonable for a Registered Dietitian or Physician to use clinical judgment in determining the method to assess body weight.

- Kistler et al, JReN 2021

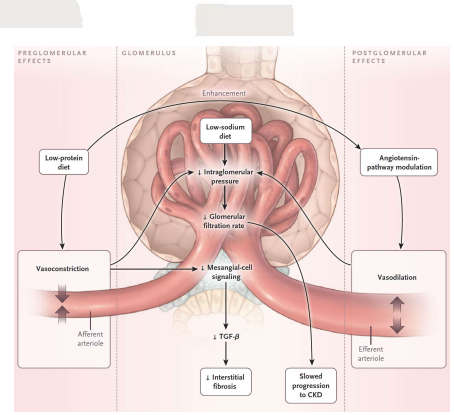
HIGH PROTEIN INTAKE

- Dilation of afferent arterioles
- Glomerular hyperfiltration
- ↑ Intraglomerular pressure

LOW PROTEIN INTAKE

- Afferent arteriole vasoconstriction
- ↓ Glomerular hyperfiltration
- ↓ Intraglomerular pressure
- ↓ Proteinuria

Glomerular hyperfiltration & hypertension are major risk factors for CKD progression.

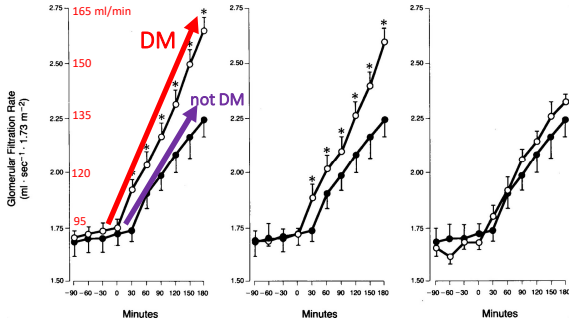


Kalantar-Zadeh & Fouque, ***N Engl J Med*** 2017

Glomerular Hyperfiltration in Diabetes/DKD

Renal hemodynamic response to a physiologic increase in plasma amino acid concentrations is augmented in diabetic patients

Figure 2. Mean (±SE) Glomerular Filtration Rate in 9 Normal Subjects (Solid Circles) and 12 Patients with Insulin-Dependent Diabetes Mellitus (Open Circles). The diabetic patients were studied before (left panel) and after (middle panel) 36 hours of strict glycemic control achieved by insulin infusion and after 3 weeks of intensive insulin therapy (right panel), whereas the normal subjects were studied once. The studies were performed after a 12-hour overnight fast. The base-line clearance periods were from —90 to 0 minutes; **amino acids were infused from 0 to 180 minutes**. Asterisks indicate a significant difference (P<0.05) between diabetic patients and normal subjects.



Tuttle … DeFronzo, N Engl J Med 1991

What is a Low and Very Low Protein Diet

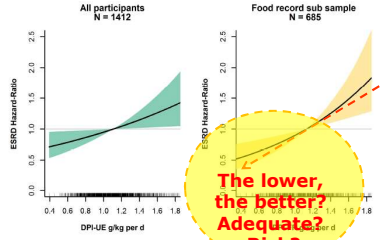
- To slow the rate of kidney failure progression over time
- To mitigate and/or control uremia:

1. *How low? :* *1.2 g/kg/day → 1.0* LPD *→ 0.8 → 0.6 →* VLPD *0.5 → 0.4 → 0.3 g/kg/day*
2. *Supplement with keto-analouges of amino acid*
3. *Risk of malnutrition / wasting*

KDOQI Renal Nutrition 2020 recommends 0.55-0.6 g/kg/day for non-diabetic NDD-CKD and 0.6 to 0.8 for diabetic CKD (DKD)

How low can Dietary Protein Intake (DPI) go?

DPI: 1.0 to 0.8 … → 0.8 to 0.6→ 0.55 → … <0.5 g/kg/day?



Metzger M, Yuan WL, Haymann J-P, Flamant M, Houillier P, Thervet E, Boffa J-J, Vrtovsnik F, Froissart M, Bankir L, Fouque D and Stengel B. **Association of a low-protein diet with slower progression of chronic kidney disease**. ***Kidney International Reports. 2017***

Most importantly, the absence of threshold for the relation between DPI and ESRD risk indicates there is no optimal DPI in the range observed in this cohort [so that even if one eats less protein than usual, e.g. going from 1.2-1.4 grams/kg/day (current average US Americans' protein intake) to 0.8-1.0 grams/kg/day, risk of ESRD is lowered]

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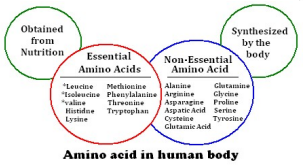
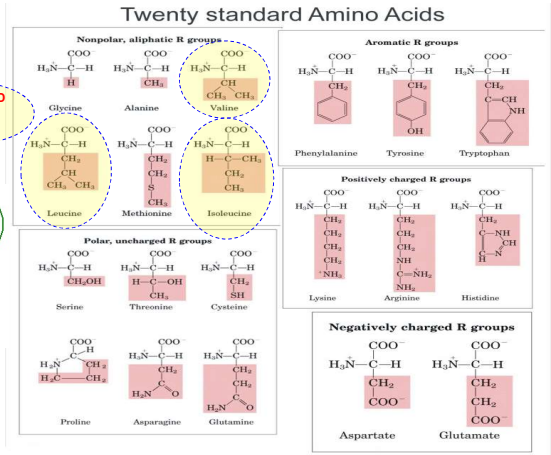
Alpha-Amino Acids

BRANCHED CHAINED AA





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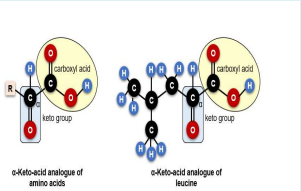
Supplemented Very Low Protein Diet sVLPD

- sVLPD is equivalent of **~0.6-0.8** g/kg/day protein
  - **0.3-0.4** g/kg/day comes from protein of any quality
  - Additional **0.3-0.4 g/kg/day** is from a supplemented mix of the 9 essential amino acids (EAAs) or of some EAAs and **ketoacid** and hydroxy-acid of the other EAAs with minimal nitrogen load

Keto-analogues of amino acids
Out of the 9 essential AAs →
4 EAAs + 4 ketoacid + 1 hydroxy-acid



Saville, W Moore, Narasaki, Kalantar-Zadeh. CJASN 2025

EAA: Essential Amnio-Acid

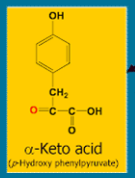
Kovesdy, Kopple & Kalantar-Zadeh. ***Am J Clin Nutr.*** **2013;97(6):1163-77**

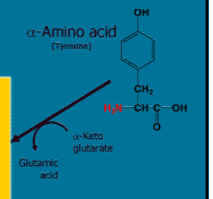
Jessiawa Saville, Linda W Moore, Yoko Narasaki, and Kam Kalantar-Zadeh. Kidney Nutrition in the Era of Value-Based Care Models: The Role of Low Protein Diets and Keto-Analogue Supplementation in Delaying Dialysis, ***CJASN* 2025** [invited lifestyle series]

@2025 K. Kalantar-Zadeh

What is a Ketoacid/Hydroxyacid Analogue of an Amino Acid?

The amiNo group is removed from the alpha carbon of the amino acid (AA) and a keto- group or hydroxy- group is substituted.



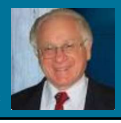


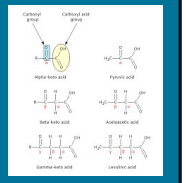
Amino Acid ↔ Ketoacid

R-C(HNH_2)COOH↔ R-(C=O)COOH

or

Hydroxyacid R-(CHOH)COOH

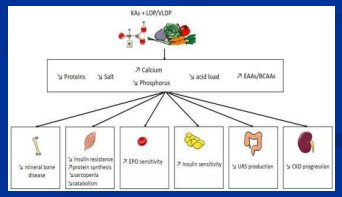




Courtesy Prof. Joel Kopple

What is a Ketoacid Supplemented Diet?

1. Usually 4 ketoacids (KAs) and 1 hydroxyacid (HA) of 5 of the essential amino acids (EAAs) (3 branched chain EAA plus phenylalanine and methionine are substituted).
2. 4 other EAAs (tryptophan, histidine, threonine and lysine) are added.
3. KAs and HAs are strong acids, hence the calcium salts of these acids are used.

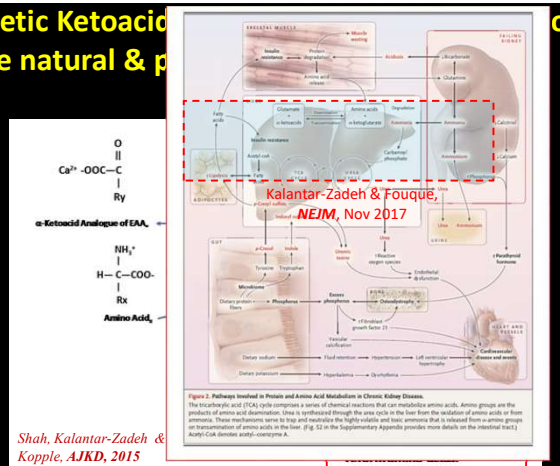


Courtesy Prof. Joel Kopple

Koppe et al, Nutrients **2019**, *11*(9), 2071,

Synthetic Ketoacid … out NITROGEN

KA are natural & p…



*Shah, Kalantar-Zadeh & Kopple, **AJKD, 2015***

*Kalantar-Zadeh & Fouque, **N Engl J Med** 2017*

18

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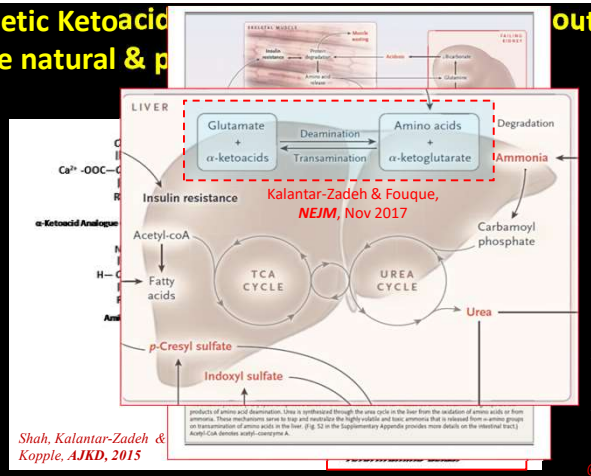

*Shah, Kalantar-Zadeh & Kopple, **AJKD, 2015***

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19

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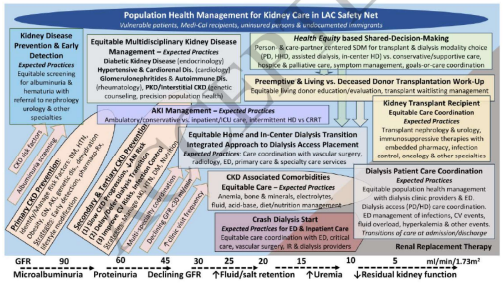
Los Angeles County Kidney Health Workgroup

Health Services LOS ANGELES COUNTY

CJASN Clinical Journal of the American Society of Nephrology

Articles Subject Collections Authors & Rev



Abbreviation: LAC: Los Angeles County, Medi-Cal, Medicaid for California residents, CKD: Chronic kidney

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PERSPECTIVE

Advancing Equitable Kidney Care through Population Health Approaches in Los Angeles County's Safety Net System

Kalantar-Zadeh, Kamyar[1,2,a]; Raff, Evan A[2,3]; Chong, Chyi-Chyi[4]; Yang, Jane K.[5]; Le, Thomas K[5]; Barba, Lilly M.[1]; Pham, Phuong-Chi[5]; Dhamija, Rajiv[6]; Ghaffari, Arshia[4]; Khine, Annika[4]; Patel, Nina[6]; Nicholas, Susanne B.[2]; Sim, John J[7]; Yee, Hal F. Jr[3]; Waltman, Belinda A.[3]; Park, Nina J.[3]

Streamlined Patient-Centric CKD Definition

Los Angeles County Kidney Care *WG*

Diabeti

- **Low**
  - **<50**
  - Based
  - Can
- **Very**
  - **<25**
    - R
    - S
- **Kidn**
- **<10%** (dialysis or preemptive transplant imminent) → Kidney Failure

REVIEW

CURRENT OPINION

Population health management of diabetic kidney disease in Los Angeles county municipal health system

Kamyar Kalantar-Zadeh[a,b,c], Theodore C. Friedman[d,e], Golriz Jafari[f], Arshia Ghaffari[g], Annika Khine[g], Susanne B. Nicholas[b], Connie M. Rhee[h], Rajiv Dhamija[i] and Evan A. Raff[g,j]

AQ1

Purpose of review
Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide, disproportionately affecting underserved and safety-net populations.

Recent findings
Los Angeles County Department of Health Services (LAC-DHS) Kidney Health Workgroup has developed

t 12 mo?"

Kalantar-Zadeh … Raff. **Population health management of diabetic kidney disease in Los Angeles county municipal health system**. ***Curr Opin Nephrol Hypertens***. **2026** Jan 1;35(1):62-71. PMID: 41263648

Harbor-UCLA MEDICAL CENTER

Division of Nephrology Hypertension and Transplantation

"Promoting Kidney Wellness"

Streamlined Patient-Centric CKD Definiti

Los Angeles County Kidney Care *WG*
Diabetic Kidney Disease (DKD) Expected Practices

- **Low Kidney Function (LKF):**
  - **<50% of normal renal function**
  - Based on at least 2 values >90 days apart
  - Can use any GFR or creatinine clearance (CrCl) equations
- **Very Low Kidney Function (VLKF)**
  - **<25% of normal renal function**
    - Refer to **dialysis access placement** **if yes answer** to: "needs dialysis in the next 12 mo?"
    - **Shared Decision Making** (SDM) for kidney care choices
  - **Kidney Dysfunction Requiring Dialysis (KDRD)**
  - **<10%** (dialysis or preemptive transplant imminent) → Kidney Failure

Kalantar-Zadeh … Raff. **Population health management of diabetic kidney disease in Los Angeles county municipal health system.** ***Curr Opin Nephrol Hypertens.*** **2026 Jan** 1;35(1):62-71. PMID: 41263048

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"Promoting Kidney Wellness"

Streamlined Patient-Centric CKD Definiti

Los Angeles County Kidney Care *WG*
Diabetic Kidney Disease (DKD) Expected Practices

- **Proteinuria**: using spot urine PCR, urine (M)ACR, or 24 hour-urine
  - *Proteinuria is the preferred metrics as opposed to albuminuria*
  - **EARLY PROTEINURIA (<1 g)**
    - ***Micro*-proteinuria: PCR >150 mg/g** or mg/day (like MACR >30 mg/g)
    - **Macro-proteinuria: PCR >0.5 g/g** or g/day (like MACR >300 mg/g, macroalbuminuria)
  - **HEAVY PROTEINURIA (1-7 g)**
    - *If* ***PCR >1 g/g (above-1-gram proteinuria):*** *may benefit from expedited nephrology referral*
    - **Nephrotic Range**: **PCR>3.5 g/g** or g/day
  - **MASSIVE PROTEINURIA (> 7g)**
    - *If* ***PCR >7 g/g (excessive proteinuria)****, nephrologist may consider renal biopsy despite clinical impression of DKD*

Kalantar-Zadeh … Raff. **Population health management of diabetic kidney disease in Los Angeles county municipal health system.** ***Curr Opin Nephrol Hypertens.*** **2026 Jan** 1;35(1):62-71. PMID: 41263048

Division of Nephrology Hypertension and Transplantation
Harbor-UCLA MEDICAL CENTER
"Promoting Kidney Wellness"

ORIGINAL INVESTIGATIONS
Pathogenesis and Treatment of Kidney Disease

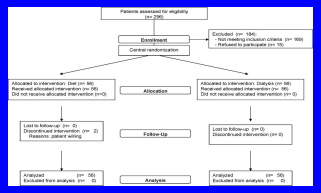
Efficacy and Safety of a Very-Low-Protein Diet When Postponing Dialysis in the Elderly: A Prospective Randomized Multicenter Controlled Study

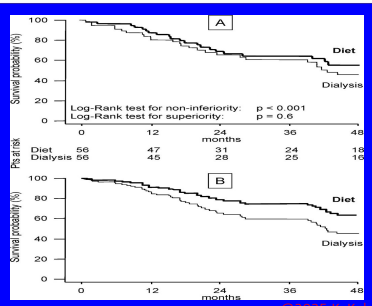
Giuliano Brunori, MD,[1] Battista F. Viola, MD,[1] Giovanni Parrinello, PhD,[2] Vincenzo De Biase, MD,[3] Giovanna Como, MD,[4] Vincenzo Franco, MD,[5] Giacomo Garibotto, MD,[6] Roberto Zubani, MD, PhD,[1,7] and Giovanni C. Cancarini, MD[1,7]

Background: A supplemented very-low-protein diet (sVLPD) seems to be safe when postponing dialysis therapy.

Brunori Study (Italy 2007)

56 uremic patients without diabetes older than 70 years with GFR 5 to 7 mL/min → randomly assigned to an sVLPD (diet group + ketoacid) versus dialysis initiation



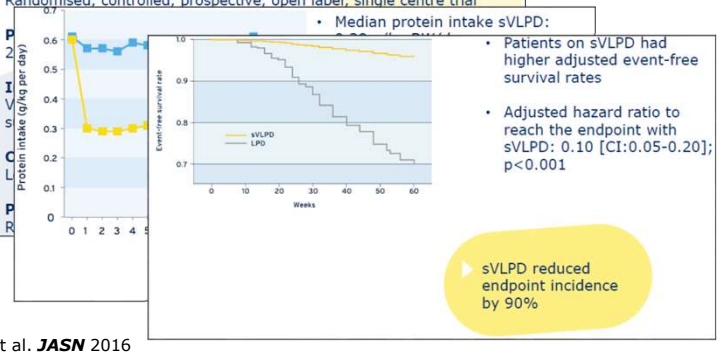


More Recent Data on Keto-analogues (Ketosteril®) and CKD Outcomes

Garneata L, Stancu A, Dragomir D, Stefan G and Mircescu G

Design
Randomised, controlled, prospective, open label, single centre trial

- Median protein intake sVLPD:
- Patients on sVLPD had higher adjusted event-free survival rates
- Adjusted hazard ratio to reach the endpoint with sVLPD: 0.10 [CI:0.05-0.20]; p<0.001



sVLPD reduced endpoint incidence by 90%

Garneata L et al. ***JASN*** 2016

Contents lists available at ScienceDirect

Clinical Nutrition 2021

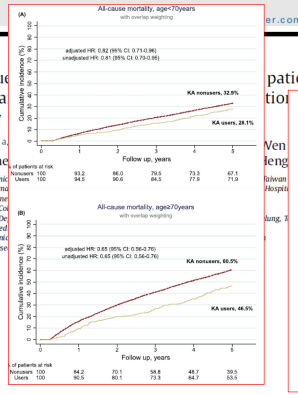
ELSEVIER

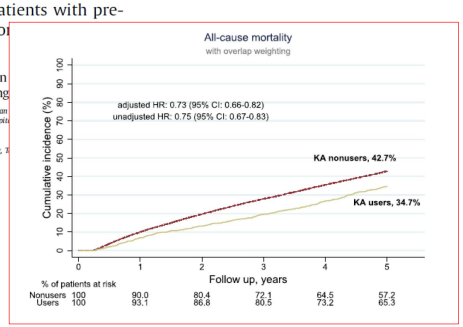
CLINICAL NUTRITION

Original article

Ketoanalogue … patients with pre-dialysis adva… based study

Hsing-Yu Chen [a], Yung-Chang Che… Ven… Feng





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7. **Liver disease** with hyperammonemia states: cirrhosis, urea cycle defects, (not nephrology)

BMC Nephrology

BMC Nephrol. 2016 Jul 7;17:62. doi: 10.1186/s12882-016-0281-z

Efficacy of the Essential Amino Acids and Keto-Analogues on the CKD progression rate in real practice in Russia - city nephrology registry data for outpatient clinic

Alexander Zemchenkov [1,2,3], Irina N Konakova [1,2]

	eGFR decline rate			Standardized effect size	
	First 5 visits	Second 5 visits	Bias corrected (Hedges)	Standard error of effect size estimate	Confidence interval for effect size
	ml/min/1.73 m² per year				
Treatment group	−2.71 ± 2.38	−2.01 ± 2.26	0.30	0.13	0.02÷0.58
Control group	−2.18 ± 2.01	−2.04 ± 2.18	0.07	0.14	−0.22÷0.35
Difference	$p = 0.10$	$p = 0.93$	$p < 0.001$		

Low protein diet (LPD), supplemented by EAA/KA, in 96 Russian patients withs CKD Stage 3B-5 was compared to GFR slope changes in the control group of 96 patients, randomly selected from matched (by gender, age, diagnosis and CKD Stage) cohort of 320 patients from the city Registry. The mean baseline eGFR was 23 ± 9 ml/min/1.73 m2; 29% CKD3B, 45% CKD4, 26% CKD5.

Results: The rate of eGFR decline changed from −2.71 ± 2.38 to −2.01 ± 2.26 ml/min/1.73 m2 per year in the treatment group and from −2.18 ± 2.01 to −2.04 ± 2.18 ml/min/1.73 m2 per year in the control group ($p = 0.04$ and $p = 0.6$).

Conclusions: LPD combined with EAA/KA supplementation led to the decrease of the CKD progression in real nephrology practice → beneficial effect of LPD supplemented by EAA/KA

OXFORD ERA nd t 2025

Nephrol Dial Transplant, 2025, **0**, 1–12

https://doi.org/10.1093/ndt/gfaf154

Advance access publication date: 15 August 2025

Cost-effectiveness of protein restricted diets in advanced CKD

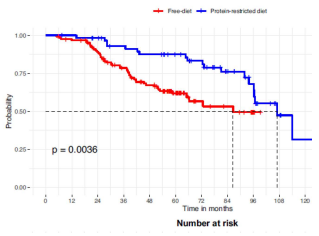
Protein-Restricted Diets (PRD): LPD and VLPD (DPI <0.8 g/kg/day)

Vincenzo Bellizzi [1], Mario Fordellone [2], Luca De Nicola [3], Roberto Minutolo [3], Simona Signoriello [2], Giuseppe Quintaliani [4], Biagio Di Iorio [5] and Paolo Chiodini [2]

[1]Department of Medical Sciences, Division of Nephrology and Dialysis, AORN "Sant'Anna e S…

223 CKD/4–5 patients adhering to PRD [VLPD 0.3 g/kg/day or LPD 0.6 g/kg/day, some supplemented with keto-analogues, followed for 5 years, assessing direct and indirect costs.

In patients adherent to diet prescription, PRD delays the start of dialysis, improves survival and saves money.

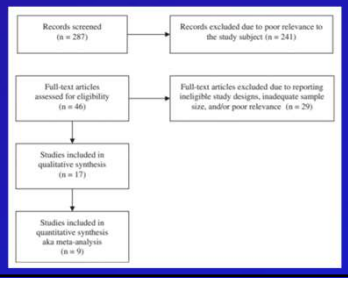


ORIGINAL ARTICLE
Journal of Cachexia, Sarcopenia and Muscle 2018; 9: 235–245
Published online 2 November 2017 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/jcsm.12264

Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials

Connie M. Rhee[1†], Seyed-Foad Ahmadi[1,2†], Csaba P. Kovesdy[3,4] & Kamyar Kalantar-Zadeh[1,2,5,6,7*]

- Meta-analysis of 16 RCT's of low protein diet in non-dialysis dependent CKD.
  - Each trial with ≥30 participants.

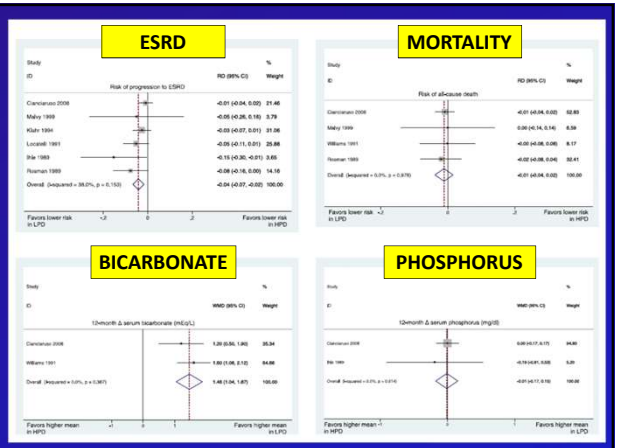


Rhee, Ahmadi, Kovesdy, Kalantar, ***JCSM*** 2018.

Low protein diet (<0.8 g/kg/day) associated with:

- ↓ ESRD
- ↓ All-cause mortality
- ↑ Serum bicarbonate
- ↓ Serum phosphorus
- ↓ Azotemia

No differences in nutritional indices



Rhee, Ahmadi, Kovesdy, Kalantar, ***JCSM*** 2018.

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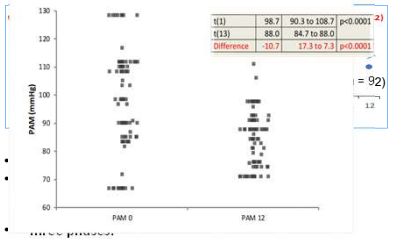
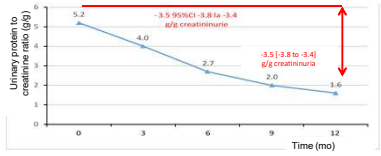
Low Protein Diet Reduces Proteinuria and Decline in Glomerular Filtration Rate in Advanced, Heavy Proteinuric Diabetic Kidney Disease

Garneata L, Mocanu CA, Mircescu G et al. ***Nutrients***, **2024**

Nutrients





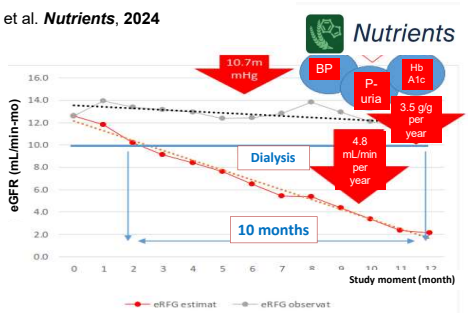
- Proteinuria significantly decreased (by 3.5g/g creatininuria).
- Blood pressure control was ameliorated (by 11 mm Hg).

Low Protein Diet Reduces Proteinuria and Decline in Glomerular Filtration Rate in Advanced, Heavy Proteinuric Diabetic Kidney Disease

Garneata L, Mocanu CA, Mircescu G et al. ***Nutrients*, 2024**

S-LPDs in advanced DKD with heavy proteinuria:

Conclusion:
LPD supplemented with KA seems effective in safely postponing KRT by reducing proteinuria and the decline in kidney function in advanced DKD.



Garneata L, Mocanu CA, Mircescu G et al. *Nutrients*, 2024

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Quantity vs Quality of Protein

PLAFOND Study (Plant Focused Nutrition for DKD, NIH R01 Study Harbor-UCLA and VA-GLA, 2023-2026)

- Is its just the "**amount**" (quantity) of Dietary Protein Intake that affects Kidney health?
- What about "**type**" (quality) of dietary protein, i.e., animal vs. plant protein?

Animal vs Plant Protein in DKD

- US population consume on average 81 g of protein per day, of which approximately 85% (69 g/day) is animal protein.
- The amount of total protein consumed by US general population greatly exceeds their requirement.

Table 1. Summarized protein consumption in US and Europe.

	Normal average protein requirement	Estimated total protein intake	Estimated animal protein intake	Estimated plant protein intake
United States	★ 8–10%Energy	81 g/day	85%	15%
Europe (average)	• Estimated average requirement: 0.66 g/kg	0.91–1.83 g/kg	55–73%	24–39%
Spain	• Recommended dietary allowance: 0.83 g/kg	94–144 g/day	73% (67–105 g/day)	24%
UK health-conscious group		60–72 g/day	17 g/day	39–51 g/day

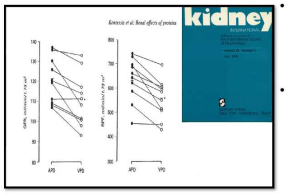
Adeva-Andany MM, Fernández-Fernández C, Carneiro-Freire N, Vila-Altesor M, Ameneiros-Rodríguez E. **The differential effect of animal versus vegetable dietary protein on the clinical manifestations of diabetic kidney disease in humans**. ***Clin Nutr ESPEN***. 2022 Apr;48:21-35.

Zoom Webinar — You are viewing K S Nayak's screen — View Options

Recording

Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins

Panayotis Kontessis, Sharon Jones, Rosemary Dodds, Roberto Trevisan, Romano Nosadini, Paola Fioretto, Mauro Borsato, Davide Saccerdoti, and GianCarlo Viberti



One of the first to identify the role of diet in CKD

- Human volunteers fed for 3 weeks with a vegetable-based diet (N = 10), an animal protein diet (N = 10) both with the same amount of total protein
- Animal-based protein diets increased GFR more than similar amounts of plant-based proteins
- Vegetable proteins seem to induce renal changes comparable to those obtained by reducing the total amount of protein in the diet and prevent the vasodilatory and proteinuric effects of meat
- **Protein modified**, rather than protein restricted, diets may prove advantageous in the long-term treatment of chronic renal failure

Unmute — Start Video — Participants — Q&A — Chat — Share Screen — Raise Hand — Record — Leave

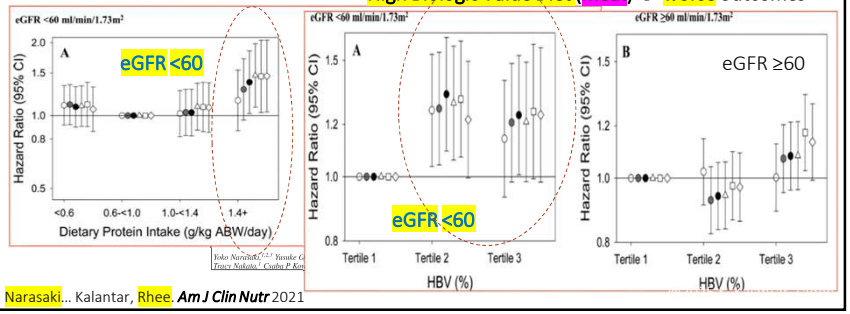
@2025 K. Kalantar-Zadeh

The American Journal of CLINICAL NUTRITION

Dietary protein intake, kidney function, and survival in a nationally representative cohort

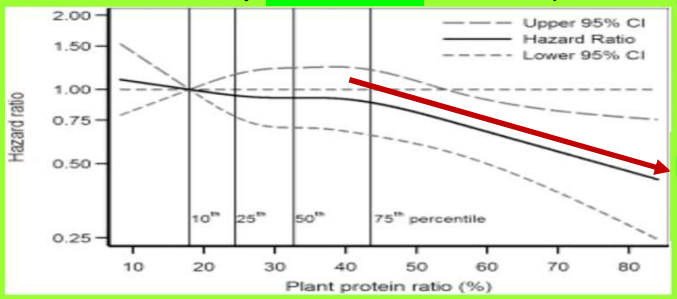
High Protein Diet → worse outcomes

High Biologic Value Diet (meat) → worse outcomes



Narasaki… Kalantar, Rhee. ***Am J Clin Nutr*** 2021

CKD Patients: ↑ Plant-Protein Ratio → ↓ Mortality?



The more plant-protein proportion, the lower CKD mortality

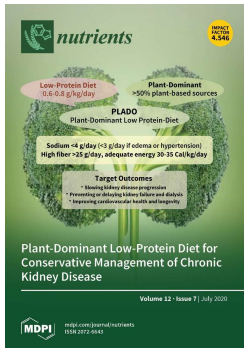
Figure 3. **Restricted cubic spline of mortality association of plant protein ratio in the estimated glomerular filtration rate < 60 mL/min/1.73 m_2 subpopulation.**

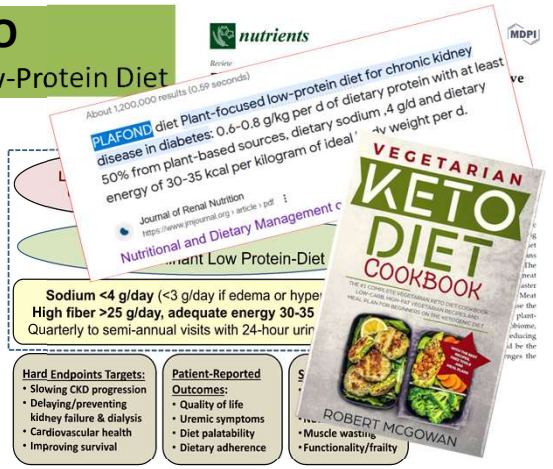
Xiaorui Chen, Guo Wei, Thunder Jalili, Julie Metos, Ajay Giri, Monique E. Cho, Robert Boucher, Tom Greene, Srinivasan Beddhu. **The Associations of Plant Protein Intake With All-Cause Mortality in CKD, *American Journal of Kidney Diseases***, 2015, http://dx.doi.org/10.1053/j.ajkd.2015.10.018

@2025 K. Kalantar-Zadeh

PLADO

Plant-Dominant Low-Protein Diet





Sodium <4 g/day (<3 g/day if edema or hype…
High fiber >25 g/day, adequate energy 30-35
Quarterly to semi-annual visits with 24-hour uri…

Hard Endpoints Targets:
- Slowing CKD progression
- Delaying/preventing kidney failure & dialysis
- Cardiovascular health
- Improving survival

Patient-Reported Outcomes:
- Quality of life
- Uremic symptoms
- Diet palatability
- Dietary adherence

- Muscle wasting
- Functionality/frailty

AKDH

A Low-Protein, Plant-Dominant Gluten-Free Diet for Immunoglobulin A Nephropathy and Focal Segmental Glomerulosclerosis

Jason Patel, Kamyar Kalantar-Zadeh, Melanie Betz, and Shivam Joshi

Table 2. Example Foods for a Gluten-Free Plant-Dominant Low-Protein (

Grain & Starch Foods	Protein Foods	Fats
Rice (all types)	Beans (all types)	Olive oil
Quinoa*	Lentils	Canola oil
Buckwheat*	Nuts (all types)	Avocado oil
Amaranth*	Seeds (all types)	Walnut oil
Millet	Tofu	Flaxseed oil
Sorghum*	Green peas	Sesame oil
Teff*		
Oats		
Corn		
Rice noodles		
Potatoes		
*Provides more than 5 g protein per 1/2 cup cooked serving		

Fruits	Vegetables
Apples	Broccoli
Bananas	Carrots
Oranges	Spinach
Grapes	Eggplant
Berries	Bell peppers
Pineapple	Cucumbers
Mango	Cauliflower
Watermelon	Kale
Kiwi	Zucchini

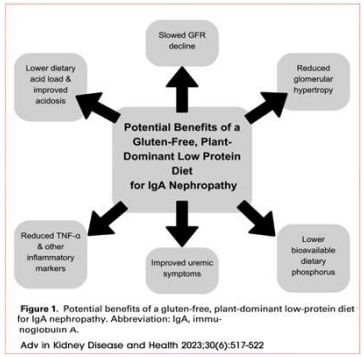


Figure 1. Potential benefits of a gluten-free, plant-dominant low-protein diet for IgA nephropathy. Abbreviation: IgA, immunoglobulin A.

Adv in Kidney Disease and Health 2023;30(6):517-522

Patel, Kalantar-Zadeh, Betz, Joshi, ***Advances in Kidney Disease Health* 2024**

Keto-analogue supplemented Vegan Diet making vegan diet even safer for CKD

JOURNAL ARTICLE

#240 Supplemented ketoanalogues (KAs) with plant versus animal based low protein diet (LPD) in non-dialysis CKD

Naveen KumarMedi, Ramphani Jasthi, Naveen Mattewada, Shivanand Nayak

Volume 40, Issue Supplement_3 October 2025

DESIGNS: Prospective observational study, from Nov 2021 to Oct 2023, involving 50 patients with non-dialysis CKD stage 3 to 5, divided into 2 groups, of 25 each and followed up for 1 year.

1) A plant-based LPD
2) Animal predominant LPD
3) Both groups LPD: 0.6 gm/kg/day and supplemented with KAs

RESULTS: Plant-based LPD, supplemented with KAs may offer comparable or even superior benefits over an animal predominant LPD in non-dialysis CKD, in safely postponing KRT to some extent.

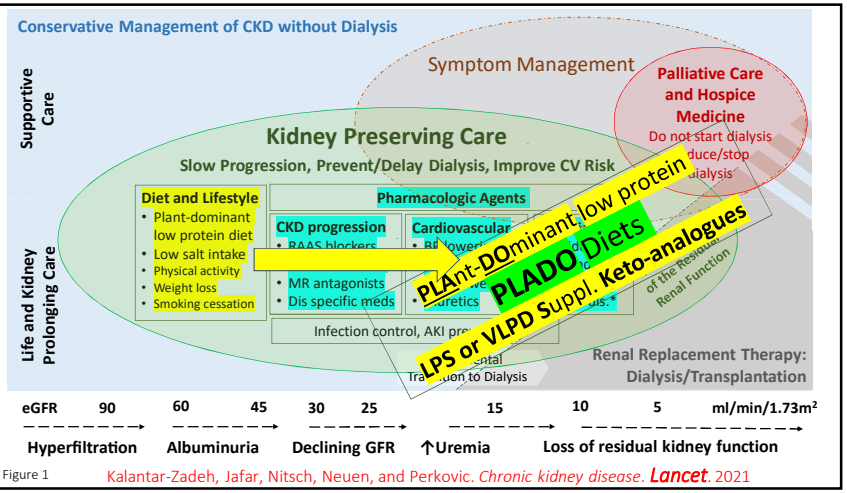


Figure 1 Kalantar-Zadeh, Jafar, Nitsch, Neuen, and Perkovic. *Chronic kidney disease.* ***Lancet***. 2021

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American Journal of Clinical Nutrition 2013

Reconciling Low Protein Intake with Nutritional Therapy:

Is there Risk of Malnutrition?

AJCN. First published ahead of print May 1, 2013 as doi: 10.3945/ajcn.112.036418.

American Journal of Clinical Nutrition 2013 AJCN 2013

Narrative Review

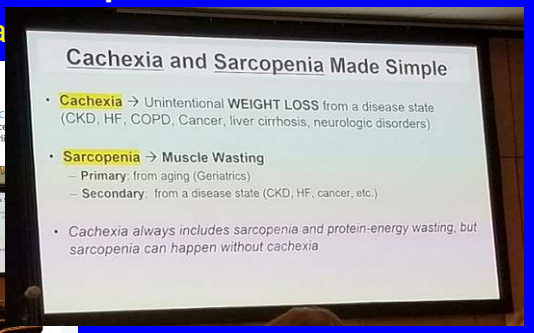
Kovesdy, Kopple and Kalantar-Zadeh
Management of PEW in NDD-CKD: Reconciling LP Intake with Nutritional Therapy

Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy[1–4]

Csaba P Kovesdy, Joel D Kopple, and Kamyar Kalantar-Zadeh

Can Low Protein Diet Cause PEW Malnutrition, Sarcopenia and Cachexia?

•Are LPD a



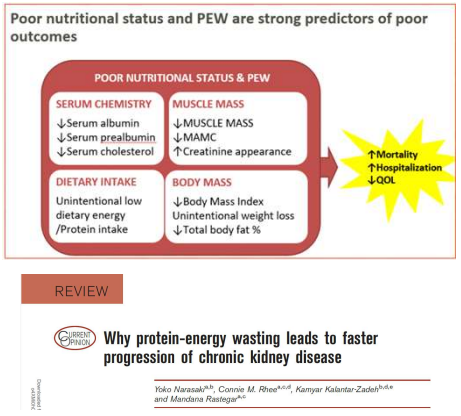
Cachexia, Sarcopenia and Wasting Disorders Conference
Dec 6-8, 2019, Berlin, Germany

Current Opinion in Nephrology and Hypertension

Why protein-energy wasting leads to faster progression of CKD

Yoko Narasaki, Connie M Rhee, Kamyar Kalantar-Zadeh, Mandana Rastegar

Current Opinion in Nephrology and Hypertension
2025 Jan 1;34(1):55-66.



Poor nutritional status, sarcopenia, and PEW are strong predictors of faster CKD progression

Indices of protein energy-wasting	Population	Author	Study design	Results
women and <7.26 kg/m2 in men)				Association of sarcopenia with eGFR was U-shaped after multivariable adjustment.
Skeletal muscle index calculated using body compositions measured by dual-energy X-ray absorptiometry	N=123 adults with NDD-CKD and N=57 adults with non-CKD	Yu *et al.* Sci Rep, 2021	Prospective cohort study (Recruited from 09/2017 to 09/2018 and followed up until 12/2019)	Skeletal muscle index showed a downward trend with CKD progression. CKD progression was an independent risk factor for sarcopenia.
Sarcopenia, low bone mineral density (BMD; osteopenia or osteoporosis), and osteosarcopenia (sarcopenia and low BMD)	N=251 adults with NDD-CKD (Age ≥65 years)	Nakano *et al.* Bone, 2024	Prospective cohort study (median follow-up of 5.2 years)	Osteosarcopenia group rather than the only low BMD or only sarcopenia groups exhibited a higher risk of (i) composite of all-cause death, initiation of KRT, and admissions owing to major adverse cardiovascular and cerebrovascular events and (ii) kidney composite outcome. Low handgrip strength was strongly associated with a high risk of (i) and (ii). BMI, skeletal muscle mass index, or BMD was not associated with lower risk of (i) nor (ii).

Narasaki, Rhee, Kalantar-Zadeh, Rastegar. Why PEW leads to Faster CKD Progression. ***Curr Opin Nephrol Hypertens* 2025**

Cause of PEW in CKD: Unintentional low dietary intake

Indices of protein energy-wasting	Population	Author	Study design	Results
Dietary intake				
DPI	*N* = 1522 adults with non-CKD (Age 45–64 years)	Cirillo *et al.* Nephrol Dial Transplant, 2014	Prospective cohort study (follow-up of 12 years)	High protein intake was associated cross-sectionally with higher GFR but longitudinally with greater GFR decline over time.
DPI	*N* = 3798 adults with non-CKD (Age 26–65 years)	Herber-Gast *et al.* Am J Clin Nutr, 2016	Prospective cohort study (follow-up of 15 years)	Higher low-fat dairy consumption (≥2 servings), but not sources of protein, was associated with less annual decline in the eGFR, particularly in individuals with a mildly decreased eGFR.
DPI	*N* = 3165 with non-CKD	Malhotra *et al.* J Ren Nutr, 2018	Prospective cohort study (median follow-up of 8.0 years)	Among African American individuals with diabetes, higher protein intake as a percentage of total energy intake was positively associated with greater decline in eGFR in analyses that accounted for risk factors for kidney disease.
DPI	*N* = 2419 with non-CKD and NDD-CKD	Beasley *et al.* J Nutr, 2011	Prospective cohort study (follow-up of 11 years)	Higher protein intake was not associated with impaired renal function among postmenopausal women without a diagnosis of chronic kidney disease.
DPI	*N* = 1594 with NDD-CKD	Metzger *et al.* Kidney Int Rep 2017	Prospective cohort study (median follow-up of 5.6 years)	Lower baseline DPI was associated with slower progression to ESKD.
DPI	*N* = 1572 adults with NDD-CKD	Lee *et al.* Nutrients, 2019	Prospective cohort study (mean follow-up of 41.6 months)	High protein intake was associated cross-sectionally with higher GFR but longitudinally with greater GFR decline over time.

BMD, bone mineral density; BMI, body mass index; DKD, diabetic kidney disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HDL, high density lipoprotein; KRT, kidney replacement therapy; LDL, low density lipoprotein; NDD-CKD, nondialysis dependent chronic kidney disease; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein; WHR, waist-to-hip ratio.

Narasaki, Rhee, Kalantar-Zadeh, Rastegar. Why PEW leads to Faster CKD Progression. ***Curr Opin Nephrol Hypertens* 2025**

ELSEVIER

Nutrition 2021

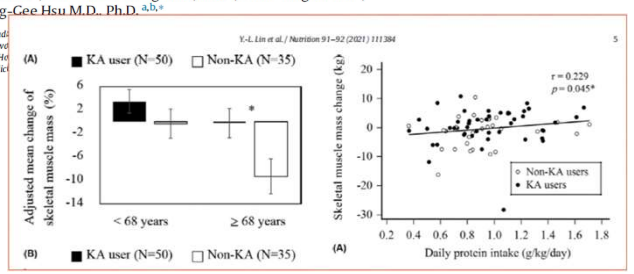
journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Effects of ketoanalogues on skeletal muscle mass in patients with advanced chronic kidney disease: real-world evidence

Yu-Li Lin M.D. [a,b], Jia-Sian Hou Ph.D. [a], Chih-Hsien Wang M.D., M.S. [a], Chen-Ying Su B.S. [c], Hung-Hsiang Liou M.D. [d,*], Bang-Gee Hsu M.D., Ph.D. [a,b,*]

[a] Division of Nephrology, Hualien Tzu Chi Hospital, Budi
[b] School of Medicine, Tzu Chi University, Hualien, Taiwa
[c] Division of Dietetics and Nutrition, Hualien Tzu Chi Ho
[d] Division of Nephrology, Department of Internal Medici



What are the indications for keto-analogues use?

LPD: Low protein Diet, VLDP: Very low Protein Diet

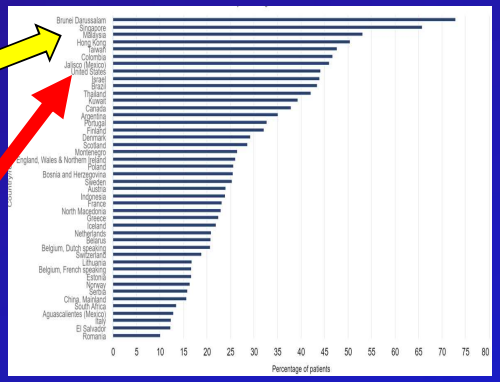
1. LPD in CKD patients (at any stage) with (or at risk of) **Malnutrition** or **Protein-Energy Wasting** (PEW)
2. VLPD in **advanced CKD** GFR <25% (very low kidney fu… *the main indication of the Fresenius Kabi product]*
3. LPD in **CKD 3-5** <50% (Low Kidney F… …planted patients with LKF
4. LPD at any CKD stage but with **"hea… proteinuria** >1g/g
5. LPD in HD and PD patients (ESRD) with **residual renal function** (RRF) for **incremental dialysis** to prolong RRF and lower dialysis dose/frequency
6. Vegan Diet (VLPD or LPD), making vegan diet safer for CKD [and for non-CKD but with **muscle-building** puposes?]
7. **Liver disease** with hyperammonemia states: cirrhosis, urea cycle defects, (not nephrology)

Combing pharmacotherapy and Keto-acid supplemented diet

International comparisons of Diabetic KD (DKD)

Brunei, Singapore, Malaysia, Taiwan with highest % of patients with incident ESRD due to DKD ~53-73%

USA 8th highest in percentage of patients with incident ESKD due to DKD



USRDS ADR 2023.

Los Angeles County Kidney Health WG

Diabetic Kidney Disease (DKD) Expected Practices (EPs)

Clinical Diagnosis of DKD without Kidney Biopsy with 4 out of 5 criteria

1. **Diabetes mellitus** current or past diagnosis, or **A1c >6%**
2. **Low Kidney Function** (**LKF**) **<50%**
3. **Proteinuria** at any level: urine PCR >150 mg/g
   If proteinuria 2 times nephrotic range (>7 g/g) → consider renal biopsy despite suspected DKD
   despite suspected DKD
4. **Documented history of microangiopathy**: 1) retinopathy, 2) neuropathy, 3) gastroparesis, or 4) diabetic foot ulcer
5. **Any of the following DKD supportive findings**:
   a) Large kidney size (>12 cm in length), or
   b) Rapid decline in renal function (>25 ml/min drop per year), or
   c) Other renal diseases are ruled out, such as via serology and/or genetic testing

Kalantar-Zadeh … Raff. **Population health management of diabetic kidney disease in Los Angeles county municipal health system**. ***Curr Opin Nephrol Hypertens***. **2026 Jan** 1;35(1):62-71. PMID: 41263046

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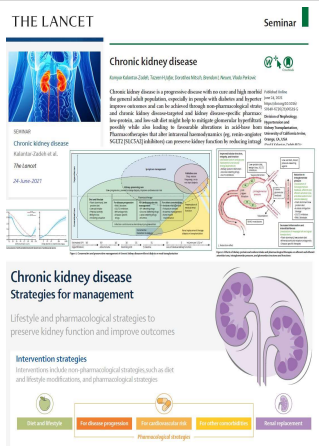
What is Preservative Management of CKD

- Kidney preserving care is a life-sustaining type of conservative management with the primary goal of **slowing CKD progression** and **preserving kidney function** to prolong dialysis-free time for as long as possible, or ideally avoid it altogether.
- This approach strives to achieve the greatest survival including improved cardiovascular health and superior health-related quality of life with effective treat… of renal and non-renal com… associ…

Preservation of kidney function can improve outcomes and may be achieved by use of :
1. **non-pharmacologic** strategies, including **dietary** adjustments, and
2. CKD-targeted and kidney disease specific **pharmacologic** interventions.



Kalantar-Zadeh K, et al. *Chronic kidney disease*. The *Lancet*. *2021*

Diabetic Kidney Disease (DKD) *Expected Practices (EPs)*

Los Angeles County Health

Kidney Disease Integrated Therapy (KDIT)

- **KDMT: Kidney Disease Medical Therapy**
- evidence-based, multi-agent *pharmaco-therapy* approach for approach for DKD, incorporating recommended therapies: therapies:
  - 1) **RAASi** (ACEi/ARB)
  - 2) **SGLT2i**
  - 3) **MRA**
  - 4) **GLP1-ra**
- **RNLM: Renal Nutrition & Lifestyle Medicine**

Kidney Health Workgroup — Health Services

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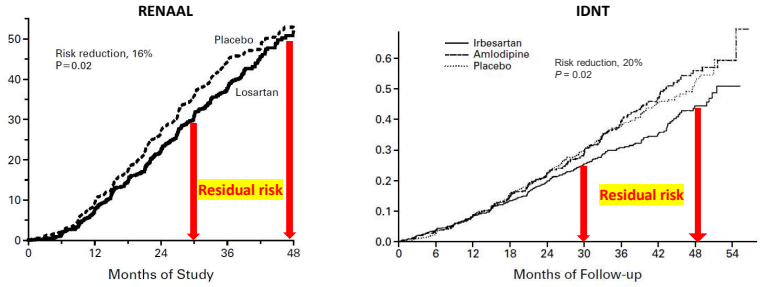
Angiotensin Receptor Blockade in Type 2 Diabetes and CKD → DKD

Doubling of serum creatinine, ESKD, or death



2.5 and 4-year absolute residual risks: ~30% and ~45%

Brenner B *et al. N Engl J Med* **2001**;345:861–869

2.5 and 4-year absolute residual risks: ~25% and ~40%

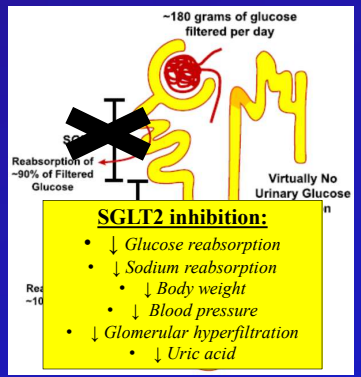
Lewis EJ *et al. N Eng J Med*. **2001**;345:851-860

SGLT2i

Courtesy Dr Connie M Rhee, VA Greater LA

Virtually all glucose filtered via glomerulus is reabsorbed

- ~180 g glucose filtered via glomerulus per day.
- 90% reabsorbed by SGLT2.
  - ➢ Proximal convoluted tubule.
- Remainder absorbed by SGLT1.
  - ➢ Descending proximal tubule straight segment.



SGLT2 inhibition:

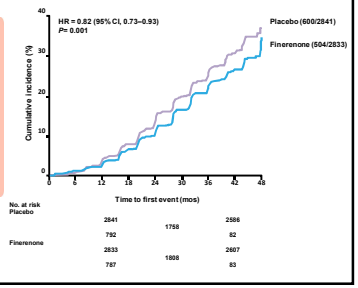
- ↓ *Glucose reabsorption*
- ↓ *Sodium reabsorption*
- ↓ *Body weight*
- ↓ *Blood pressure*
- ↓ *Glomerular hyperfiltration*
- ↓ *Uric acid*

Neumiller and Tuttle, ***JASN*** 2017.
Rhee, Kalantar-Zadeh, Tuttle, ***Curr Opin Neph HTN*** 2022.
Rhee et al, ***Sem Dial*** 2014.

MRA use in Patients with Diabetes and CKD

We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥ 3mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.

K^+ ≤4.8 mmol/l	K^+ 4.9–5.5 mmol/l	K^+ >5.5 mmol/l
• Initiate finerenone - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2 - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2 • Monitor K^+ at 1 month after initiation and then every 4 months • Increase dose to 20 mg daily, if on 10 mg daily • Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l	• Continue finerenone 10 mg or 20 mg • Monitor K^+ every 4 months	• Hold finerenone • Consider adjustments to diet or concomitant medications to mitigate hyperkalemia • Recheck K^+ • Consider reinitiation if/when K^+ ≤5.0 mmol/l



Courtesy Sankar D Navaneethan, MD, MS, MPH

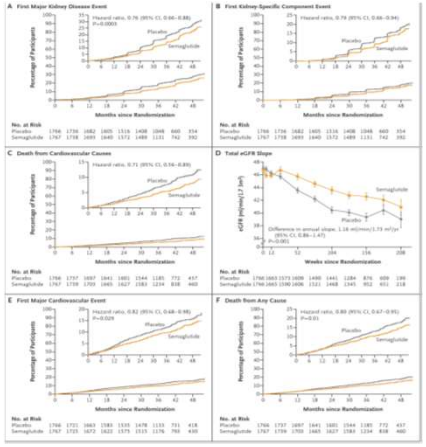
GLP1-RA


The NEW ENGLAND JOURNAL of MEDICINE

JULY 11, 2024

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

MUSCLE LOSS UP TO 30 !!!



Potential combined effects of SGLT2i and protein reduction

Low protein diet has a range of effects that aligns with those of SGLT2i

In addition, they target common metabolic derangements of advanced CKD like reduced acidosis and phosphatemia.

Beneficial effects of sodium-glucose-transporter 2 (SGLT2) inhibitors and low-protein/plant-based diets

Effect	SGLT2 inhibitors	Low-protein/ Plant-based diet
Decreased sodium proximal tubular reabsorption	+	+
Restoration of the tubuloglomerular feedback	+*	+
Reduction of glomerular hyperfiltration	+	+
Restoration of autophagy	+*	+
Slowing of CKD progression	+*	+
Reduction of cardiovascular outcomes	+*	+*
Reduction of proteinuria	+	+*
Reduction of acid load	-	+
Reduction of phosphate load	-	+

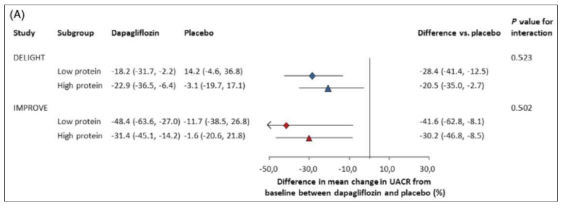
Present: +; Absent: -; * evidence from more than 1 study

Cupisti, A. et al. Front Med. 2020

Potential combined effects of SGLT2i and protein reduction

The post hoc-analysis by Van der Aart et al.[1] was re-analysed by Kalantar-Zadeh and Fouque:

- Two of three studies show a trend in favour of the low protein group[2]
- Actual low protein intake in the studies was up to the higher limit of LPD with 0.53–0.85 g/kg BW/d[3]



The current study evidence does not allow a final verdict if there is a synergy between SGLT2i and low protein intake

1) Van der Aart, AB. et al. ***Diabetes Obes Metab***. 2021,
2) Kalantar-Zadeh, K. et al. ***Diabetes Obes Metab***. 2021,
3) calculated from median daily intake and mean body weight

Combining Ketoacid Analog Supplemented Low-Protein Diets with Sodium-Glucose Cotransporter-2 Inhibitors for Patients with Diabetic Kidney Disease

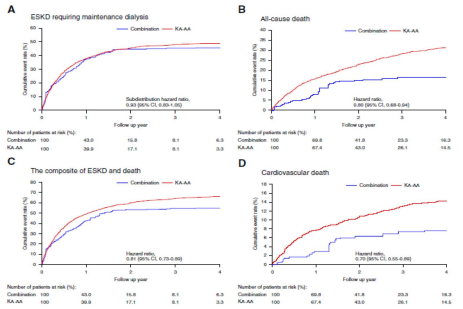
CJASN 2025-2026.

CJASN
Clinical Journal of the American Society of Nephrology

Chieh-Li Yen,[1,2] Pei-Chun Fan,[1,2] Cheng-Chia Lee,[1,2] Jia-Jin Chen,[1,2] Yueh-An Lu,[1,2] Yi-Ran Tu,[1,2] Pao-Hsien Chu,[2,3] Ching-Chung Hsiao,[1,2] Yung-Chang Chen,[1,2] and Chih-Hsiang Chang[1,2]

Key Points

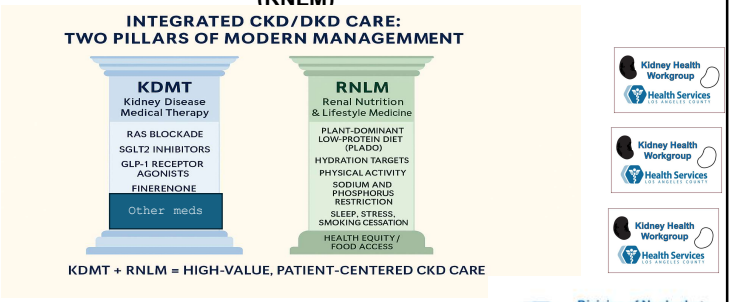
1. THE COMBINED EFFECT OF SGLT2IS AND KA-AA—SUPPLEMENTED LOW-PROTEIN DIETS HAS RARELY BEEN STUDIED.
2. THIS COHORT INCLUDED 1,729 TYPE 2 DM PATIENTS WITH EGFR <30 WHO NEWLY RECEIVED KAAA SUPPLEMENTED LOW PROTEIN DIET (SLPD), WITH OR WITHOUT SGLT2I.
3. THE COMBINATION OF SGLT2IS AND KA-AA SLPD IS LINKED TO LOWER ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY THAN KAAA SLPD ALONE.



Los Angeles County Health

Kidney Disease Integrated Therapy (KDIT)

Kidney Disease Medical Therapy (KDMT) + Renal Nutrition & Lifestyle Medicine (RNLM)



Kidney Health Workgroup
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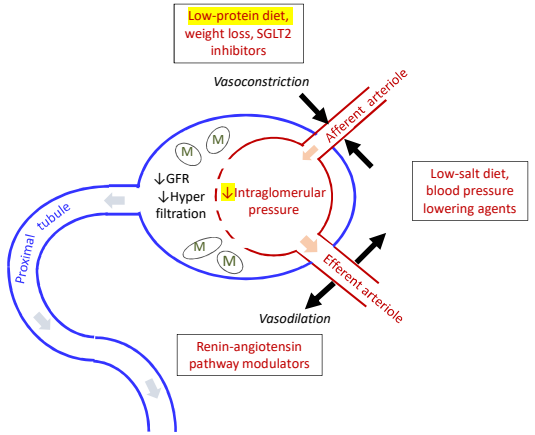
An Integrated Multimodal Approach to CKD Management

Kalantar-Zadeh, Jafar, Nitsch, Neuen, and Perkovic. *Chronic kidney disease*. ***Lancet***. 2021



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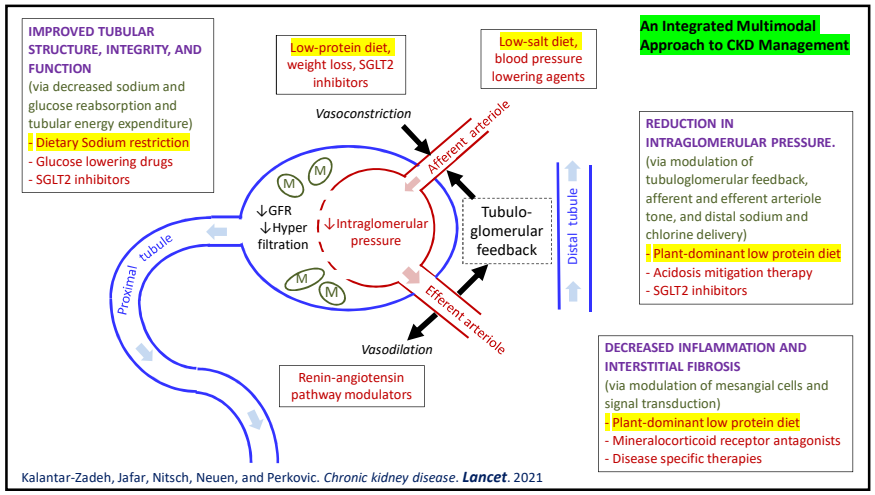

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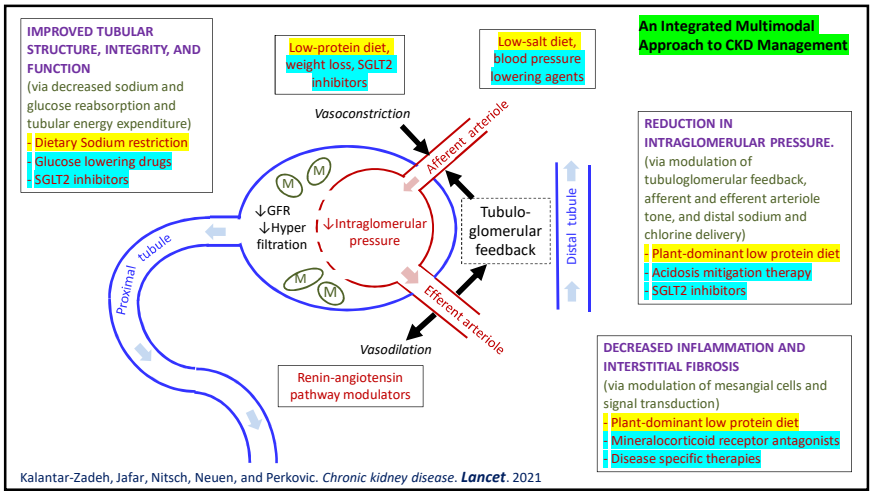

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Kidney Nutrition for Value-Based Care Models: The Role of Low Protein Diets and Keto-Analogue Supplementation to Delay Dialysis

Reduce Nitrogen Waste

Table 2. Advantages and challenges of pharmacotherapy and supplemented very low protein diet to slow progression to dialysis initiation in persons with very low kidney function

Variable	Advantages	Limitations and Risks
RAAS modulators including ACE inhibitors and ARB	Lower BP, slow CKD progression	Hyperkalemia, increased serum creatinine, AKI events, and angioedema; they often had to be discontinued in far-advanced CKD[69]
SGLT2 inhibitors	Slows CKD progression and improves glycemic control and heart failure[4]	Genital and urinary tract infection from glycosuria, ketoacidosis, volume depletion, increased serum creatinine, and AKI[70]
GLP1-RA	Useful for weight management and diabetes control, slows CKD progression	GI symptoms, diminished appetite, weight loss, risk of hypoglycemia in burnt-out diabetes[70]
Nonsteroidal MRA	Slow CKD progression in CKD with diabetes[70]	Hyperkalemia, AKI events.[70]
SVLPD	Patient-centered and aligned with lifestyle medicine and can be given without above pharmacotherapy	Risk of PEW if not correctly supplemented.[35] LPD can also cause a GFR drop[29]

ACE, angiotensin-converting enzyme; ARB, angiotensin Receptor Blocker; GI, gastrointestinal; GLP1-RA, glucagon like peptide 2 receptor; LPD, low-protein diet; MRA, mineralocorticoid receptor antagonist; PEW, protein-energy wasting; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter 2; SVLPD, supplemented very low-protein diet.

MUSCLE LOSS!!!

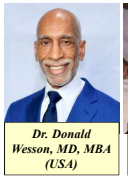
MUSCLE LOSS!!!

CJASN

onceptual model of clinical benefits of a VLPD supplemented with keto-analogues.

Saville … Kalantar-Zadeh. ***CJASN*** 2025-2026

CJASN "Lifestyle Medicine & Kidney Health" Series 2025-2026



Dr. Donald Wesson, MD, MBA (USA)

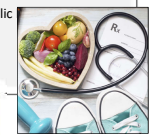
Dr. Mona Boaz, PhD, RD (Israel)

Dr. Jaimon Kelly, PhD, RD (Australia)

Dr. Kamyar Kalantar-Zadeh, MD, MPH, PhD (Editor-at-Large)

18 ARTICLE SERIES HIGHLIGHTS....

- Introduction to Lifestyle Medicine & Kidney Health
- Nutrition across the lifespan in CKD
- Race, socioeconomic status, & diet in kidney disease
- Food & nutrition insecurity in kidney disease
- Prescribing a personalized exercise program in CKD patients
- Physical activity & exercise for cardio-metabolic health in CKD
- Plant-based diets across the spectrum of kidney disease
- Dietary protein intake in CKD, from quantity to quality
- Dietary intake & the gut microbiome in CKD
- Stress management, mindfulness, & spirituality in CKD
- Dietary phosphate in kidney disease
- Obesity & metabolic health in CKD
- Ultra-processed food & food additives in CKD
- Role of nutrition in value-based care
- Sleep, circadian rhythm, & cardio-kidney-metabolic
- Culinary medicine & healthy cooking in CKD
- Precision nutrition & kidney health
- Application of novel nutritional tools in CKD



CJASN

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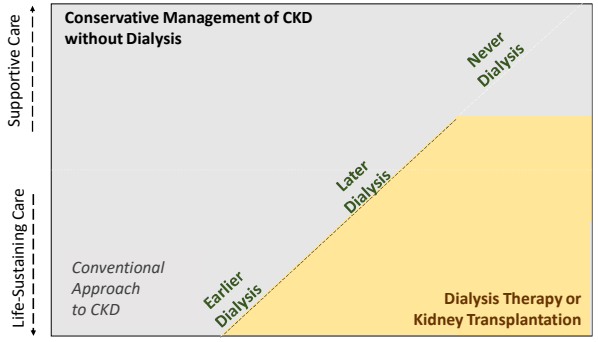
Kidney Care Chart: Conceptual Model of the Conservative Management of Advanced CKD



The New England Journal of Medicine
Kalantar-Zadeh, Wightman and Liao. *N Engl J Med* 2020;383:99-101.

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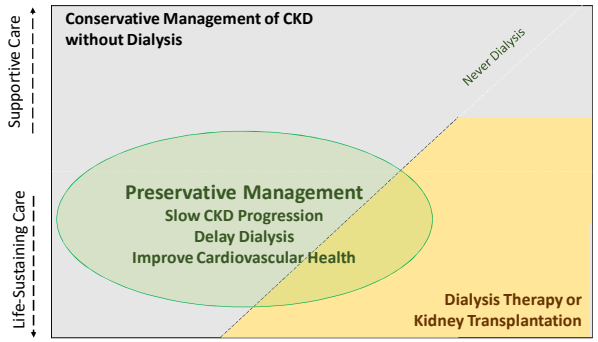

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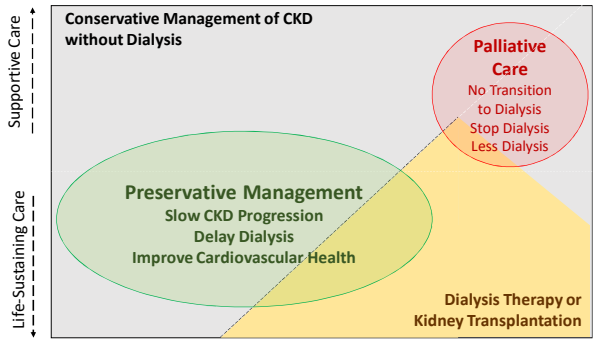

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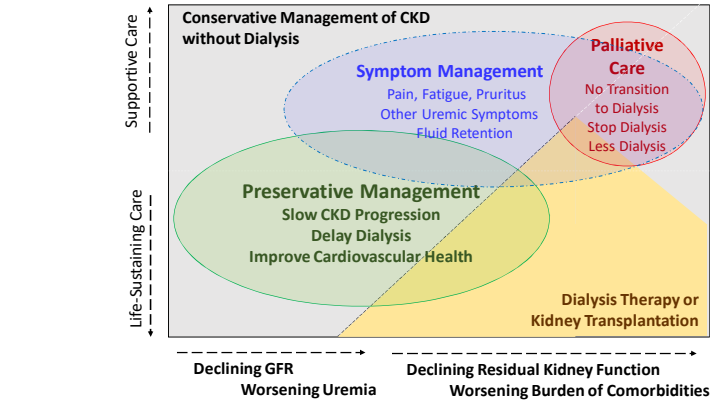

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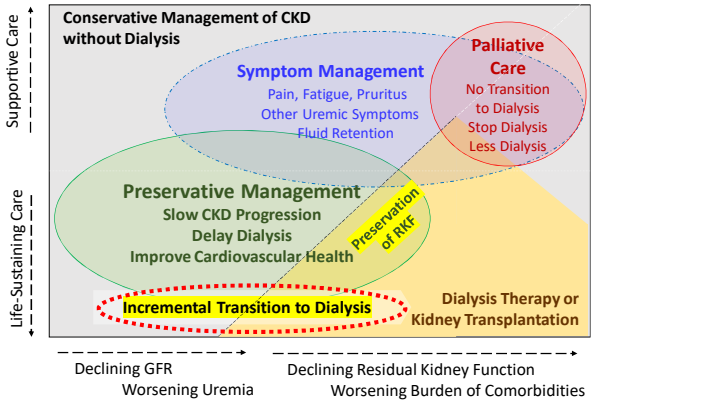

The NEW ENGLAND JOURNAL of MEDICINE

Kalantar-Zadeh, Wightman and Liao. *N Engl J Med* 2020;383:99-101.

KIDNEY RESEARCH AND CLINICAL PRACTICE — Science Citation Index Expanded (SCIE)

Personalized nutritional management in the transition from non-dialysis dependent chronic kidney disease to dialysis

Yoko Narasaki, Man Kit Siu, Matthew Nguyen,
Kamyar Kalantar-Zadeh, Connie M. Rhee

Kidney Research and Clinical Practice
2024;43(5):575-585.

Review Article

Kidney Res Clin Pract 2024;43(5):575-585
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KIDNEY RESEARCH AND CLINICAL PRACTICE

Personalized nutritional management in the transition from non-dialysis dependent chronic kidney disease to dialysis

Yoko Narasaki[1,2], Man Kit Siu[1,2], Matthew Nguyen[1], Kamyar Kalantar-Zadeh[1,2,3], Connie M. Rhee[1,2]

Main Components of Nutritional management in Advanced CKD in Anticipation of Transition to (Incremental) Dialysis

Low protein diets

- ↓ CKD progression
- Delaying dialysis initiation
- ↓ mortality risk
  - Slow eGFR decline
  - ↓ hemodynamic changes and glomerular hyperfiltration

Plant-based diets
PLADO
PLAFOND

- ↓ incident CKD
- ↓ CKD progression
- ↓ mortality risk
- ↓ CKD-related complications
  - Mineral bone disease, metabolic acidosis, uremic toxin

Potassium intake from plant-based diets

- Favorable impact on kidney and cardiac health

Sodium restriction

- Improve blood pressure and CKD progression

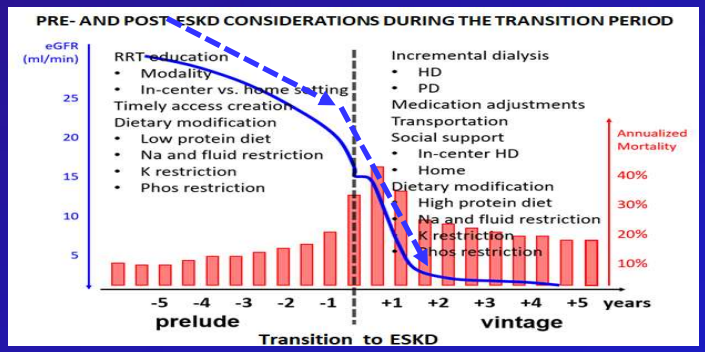
Dietary patterns

↑veges/fruits/legumes/nuts/whole grains/fish/low-fat dairy products
↓red/processed meats, Na, sugar-sweetened beverages

- Favorable on kidney health

Narasaki, Siu, Nguyen, Kalantar-Zadeh. Rhee. ***Kidney Res Clin Pract*** 2024

Sudden Drop in Residual Renal Function upon Transition to Dialysis



Rhee, Obi, Mathew, Kalantar-Zadeh, ***Sem Dial*** 2018.

transition

- *[tran-zish-uh n, -sish-]*
- noun 1. *movement, passage, or change from one position, state, stage, subject, concept, etc., to another;*
- "the transition from adolescence to adulthood."

– Dictionary.com

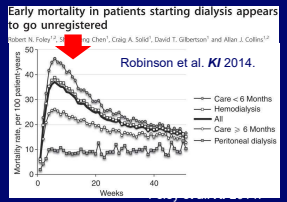
start

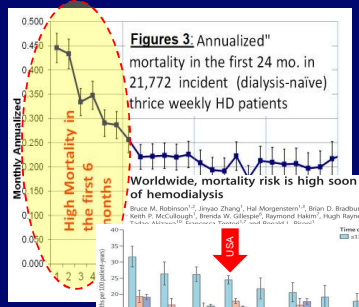
- *[stahrt]*
- 1. to begin or set out, as on a journey or activity.
- 2. to appear or come suddenly into action, life, view, etc.; rise or issue suddenly forth.
- 3. to spring, move, or dart suddenly from a position or place: The rabbit started from the bush.
- 4. to be among the entrants in a race or the initial participants in a game or contest.
- 5. to give a sudden, involuntary jerk, jump, or twitch, as from a shock of surprise, alarm, or pain: The sudden clap of thunder caused everyone to start.

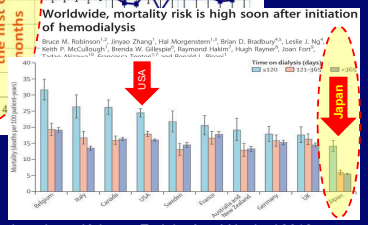
Kalantar-Zadeh et al. NDT 2017 [Blueprint of TC-CKD]

Challenges of Transition to Dialysis: Very High Early Mortality after Transition

The first 3-6 months of dialysis is associated with an even higher risk of death compared to prevalent dialysis patients.







Lukowsky … Kalantar-Zadeh, *Am J Nephrol* 2012

OPTIONS rather than dichotomy:

Dialysis therapy versus palliative care without dialysis

1. Conservative and preservative management of CKD to delay dialysis initiation, including use of *diet and lifestyle* modifications, conventional and new pharmacotherapies, and proactive symptoms management such as pain and fatigue, as well as mental health issues.
2. **Gradual transition to dialysis:** Initiating once- to twice-weekly hemodialysis or less-than-daily peritoneal dialysis at home, each of which may preserve Residual Renal Function longer than conventional dialysis.
3. Expanded use of palliative care: Instead of having a one-time palliative care consult during an inpatient hospitalization, a dialysis patient or potential candidate for dialysis could be evaluated for concurrent palliative options and symptom management as an outpatient and then during each hospitalization, independent of the severity of the person's illness.
4. Palliative dialysis with a gradual decrease in frequency and intensity: Patients and caregivers can choose less-stringent dialysis therapy with a goal of improving comfort. Dialysis could be combined with hospice care, and home dialysis could be offered at nursing homes or skilled nursing facilities. In these contexts, a focus on symptom management — rather than aggressive clearance or rigorous fluid removal — is prudent.

Kalantar-Zadeh, Wightman and Liao. ***N Engl J Med*** 2020;383:99-101.

Incremental (Gradual) Transition to Dialysis and the important role of Residual Renal Function

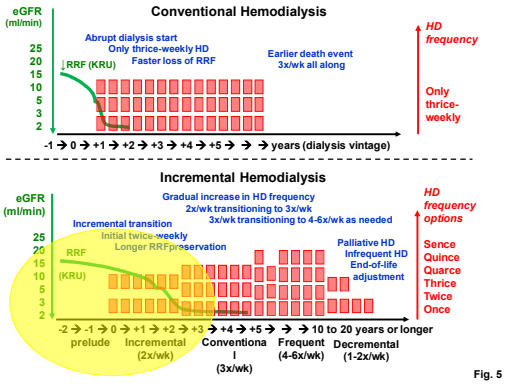


Fig. 5

Twice-weekly data from China

Cohort derived from 15 units randomly selected from each of 3 major cities (total N = 45), we generated a propensity score for the probability of dialysis frequency assignment, estimated a survival function by propensity score quintiles, and averaged stratum-specific survival functions to generate mean survival time. We used the proportional rates model to assess hospitalizations. We stratified all analyses by RRF, as reported by patients (urine output <1 vs. ≥1 cup/day).

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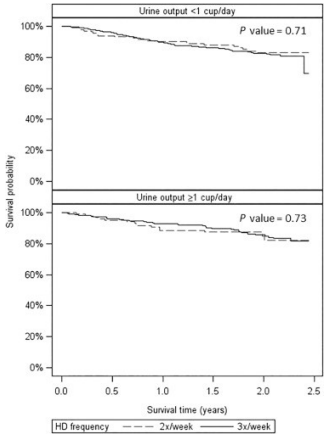
Yan…Anand

Kidney Int Rep 2018

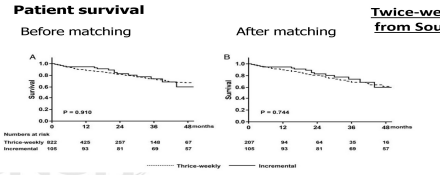


Twice-weekly data from South Korea

Nephrol Dial Transplant (2017) 32: 355–363
doi: 10.1093/ndt/gfw332
Advance Access publication 28 September 2016

Comparison of outcomes between the incremental and thrice-weekly initiation of hemodialysis: a propensity-matched study of a prospective cohort in Korea

Ji In Park[1,2], Jung Tak Park[2,3], Yong-Lim Kim[2,4], Shin-Wook Kang[2,3], Chul Woo Yang[2,5], Nam-Ho Kim[2,6], Yun Kyu Oh[2,7], Chun Soo Lim[2,7], Yon Su Kim[2,8] and Jung Pyo Lee[2,7] on behalf of the CRC for ESRD Investigators



IncHVets Trial 2022-2027

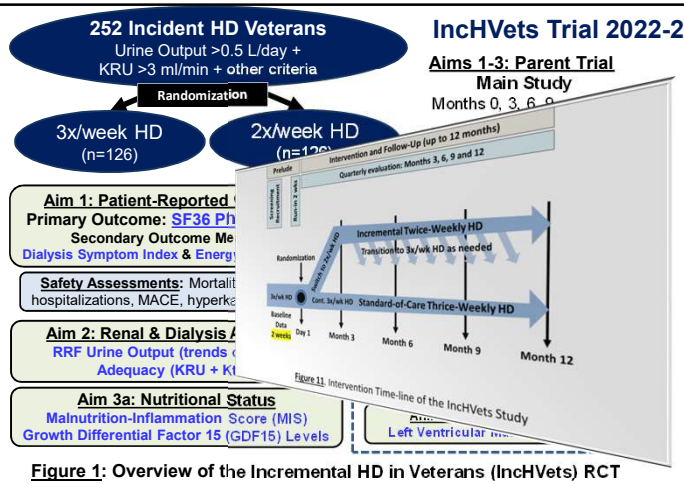


Figure 1: Intervention Time-line of the IncHVets Study

Figure 1: Overview of the Incremental HD in Veterans (IncHVets) RCT

Combined Therapy for Selected Chronic Uremic Patients: Infrequent Hemodialysis and Nutritional Management

E. Morelli, R. Baldi, G. Barsotti, F. Ciardella, A. Cupisti, L. Dani, A. Mantovanelli, S. Giovannetti
I^a Clinica Medica, Università di Pisa, Italia

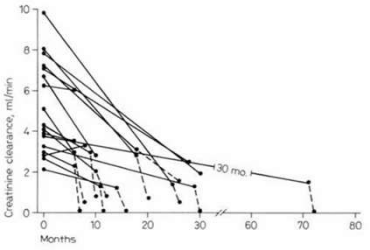


Fig. 1. Progression of renal failure as indicated by the changes of creatinine clearance rates in patients while on combined therapy (——) and when changed to conventional MHD (- - - -).

SETTING:
Combined nutritional (vegan 0.3 g/kg/day plus essential amino acid or keto-analoques) and once a week hemodialysis employed in 17 ESRD for a mean period of 18.2 months/patient vs the standard thrice-a-week dialysis schedule and free diet.

FINDINGS
The residual renal function of patients on combined therapy declined at a slower rate than in those on thrice-a-week dialysis. It is concluded that this combined therapy is a valid alternative to the conventional thrice-a-week hemodialysis and free diet for selected patients and for periods of time whose duration is conditioned by the rate of decline of the residual renal function.

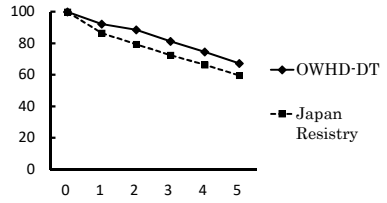
Nephron 47: 161-166(1987)

Japanese Approach: Once-weekly hemodialysis combined with low-protein and low-salt dietary treatment

as a favorable therapeutic modality for selected patients with end-stage renal failure: a prospective observational study in Japanese patients

Nakao T, Kanazawa Y, Takahashi T

Organization for Kidney and Metabolic Disease Treatment



BMC Nephrology 2018; 19: 151 Nakao T, et al: BMC Nephrol, 2018; 19:151

Caria et al. BMC Nephrology 2014, 15:172
http://www.biomedcentral.com/1471-2369/15/172
BMC Nephrology

The incremental treatment of ESRD: a low-protein diet combined with weekly hemodialysis may be beneficial for selected patients

Stefania Caria[1*], Adamasco Cupisti[2], Giovanna Sau[3] and Piergiorgio Bolasco[1]

- LPD enables to adapt infrequent dialysis
  - **24-months multicenter prospective study with 68 CKD-5 patients.**
  - **Once weekly dialysis with LPD under dietitian counselling (CDDP) *vs.* thrice weekly dialysis (THD)**

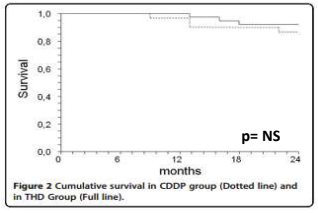


Figure 2 Cumulative survival in CDDP group (Dotted line) and in THD Group (Full line).

- **Survival in 24 months was not different (94.7% vs 86.8% in CDDP vs THD).**
- **However, hospitalization, prescribed medications and medical cost were higher in pts with thrice weekly dialysis.**

Caria S et al. BMC nephrol 2014

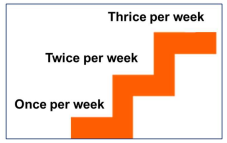
Nutritional Management of Incremental HD: strategies for dialysis commencing: once weekly → 2x/week → 3x/week

	Once-a-week	Twice-a-week	Thrice-a-week
Nutritional support	+++	++	+
Protein intake	Reduced (6 out of 7 days): sVLPD	Reduced (5 days): sVLDP or LPD	increased
Energy intake	increased	increased	increased
vascular access compromise	+	++	+++
Protection of residual renal function	+++	++	-/+
"Counter-Physiologic" effect of HD treatment	+	++	+++
HD scheduling challenge	+	++	-
Costs and reimbursement	+	++	+++

Modified from:
*Caria S, Cupisti A Sau, Bolasco. **BMC Nephrol 2014**;15:172*
*Bolasco, Cupisti, Locarelli, Caria, Kalantar-Zadeh, **J Ren Nutr**. **2016** 26:352-359*

Article 23 July 2025

Stepwise Incremental Hemodialysis and Low-Protein Diet Supplemented with Keto-Analogues Preserve Residual Kidney Function: A Randomized Controlled Trial †



Nutrients Thailand Study 2025

Piyawan Kittiskulnam[1,2,3], Khajohn Tiranathanagul[2], Paweena Susantitaphong[2,4], Jeerath Phannajit[2,4,5], Yuda Chongpison[6], Pagaporn Asavapujanamanee[7], Bongkod Surattichaiyakul[8], Kullaya Takkavatakarn[2], Pisut Katavetin[2], Kamonchanok Metta[2] and Kearkiat Praditpornsilpa[2,*]

METHODS:
30 VLKF patients with eGFR 5–10 mL/min and urine output of ≥800 mL/day → randomly assigned to receive:
1) **once-weekly HD** combined with **low-protein diet** (0.6 g/kg/day) supplemented **keto-analogues** (KAs) 0.12 g/kg/day.
2) **twice-weekly HD** with a **regular-protein diet**.

RESULTS: After 3 months, urine volume was significantly higher in the 1-Weekly HD group than in the 2-Weekly HD group (1921 ± 767 mL/day vs. 1305 ± 599 mL/day, p = 0.02),

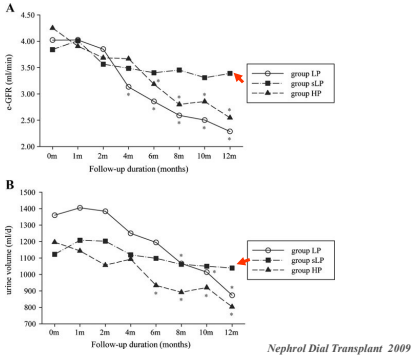
Conclusions:
Incremental HD, starting with once-weekly HD combined with protein restriction supplemented with KAs, appears to better preserve RKF among incident HD patients compared to twice-weekly HD with a regular-protein diet.

Low Protein Diet (LPD): 0.6-0.8 g/kg/day

Better Preserving RKF in PD patients by mLPD + KA
A Study From Shanghai Renji Hospital, China

eGFR

Urine Output



Nephrol Dial Transplant 2009

Low Protein Diet (LPD): 0.6-0.8 g/kg/day

Better Preserving RKF in PD patients by mLPD + KA
A Study From Shanghai Renji Hospital, China

Better preservation of residual renal function in peritoneal dialysis patients treated with a low-protein diet supplemented with keto acids: a prospective, randomized trial

Na Jiang[1], Jiaqi Qian[1], Weilan Sun[1], Aiwu Lin[1], Liou Cao[1], Qin Wang[1], Zhaohui Ni[1], Yanping Wan[2], Bengt Linholm[3], Jonas Axelsson[3] and Qiang Yao[1]

Study design:

(1) A short-term nitrogen balance study

34 PD patients were randomized to receive in-centre diets containing 1.2, 0.9 or 0.6 g of protein/kg IBW/day for 10 days

(2) A 12-month prospective study

60 PD patients were randomized to receive either a low- , keto acid-supplemented low- or high-protein diet

Nephrol Dial Transplant 2009

Low Protein Diet (LPD): 0.6-0.8 g/kg/day

Better Preserving RKF in PD patients by mLPD + KA
A Study From Shanghai Renji Hospital, China

- **The use of low-protein diets (0.6-0.8g/kg/day) supplmented with keto acids in new PD patients may both be safe from a nutritional point of view and also lead to better preservation of RKF.**

Nephrol Dial Transplant 2009

Low Protein Diet for CKD-ESRD Transition

Table 2. Recommended Dietary and Nutrient Intake in Adults, According to the CKD Stage.*

Dietary Constituent	Normal Kidney Function with Increased CKD Risk	Mild-to-Moderate CKD†	Advanced CKD†	Transition to Dialysis†	Ongoing Dialysis or Any Stage with Existing or Imminent PEW
Protein (g/kg/day)	<1.0; increase proportion of plant-based proteins	<1.0 (consider 0.6–0.8 if eGFR <45 ml/min/1.73 m² or rapid progression)	0.6–0.8, including 50% HBV protein, or <0.6 with addition of EAA or KA	0.6–0.8 on nondialysis days and >1.0 on dialysis days	1.2–1.4; may require >1.5 if hypercatabolic state develops
	tion (>50%) of plant-based foods (e.g., DASH diet)	tion (>50%) of plant-based foods	plant-based foods		ing strict vegan diet
Energy (kcal/kg/day)**	30–35; adjust to target weight reduction if BMI >30††	30–35; increase proportion with LPD	30–35; increase proportion with LPD	30–35	30–35; target higher intake if PEW present or imminent
	nsaturated saturated lipids, n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids

an estimated GFR (eGFR) of at least 60 ml per minute per 1.73 m² of body-surface area. Patients in this category do not have substantial protein- l because of another condition (e.g., diabetes, hypertension, or polycystic kidney) or a solitary kidney. (A solitary kidney can be a congenital or ac- sphrectomy for donation or cancer treatment.) Mild-to-moderate CKD is defined as an eGFR of 30 to less than 60 ml per minute per 1.73 m² with- protein per day). Patients with advanced CKD have an eGFR of less than 30 ml per minute per 1.73 m² or substantial proteinuria (>0.3 g per day). apy usually have good residual kidney function. Protein–energy wasting (PEW) is defined according to the criteria of the International Society of the denominator of the dietary recommendations for protein and energy, kg denotes the ideal body weight (IBW), especially for persons with a kilograms divided by the square of the height in meters) above 30. The IBW can be estimated in males as 50.0 kg + 2.3 kg for each inch over 5 ft emales as 45.5 kg + 2.3 kg for each inch over 5 ft. To convert phosphorus to millimoles per day, multiply by .03229. To convert calcium to milli- ASH denotes Dietary Approaches to Stop Hypertension.

Kalantar-Zadeh & Foque, **Nutritional Management of CKD**. ***NEJM*** Nov 2, 2017

NEJM, July 9, 2020, Perspective

Ensuring Choice for People with Kidney Failure — Dialysis, Supportive Care, and Hope

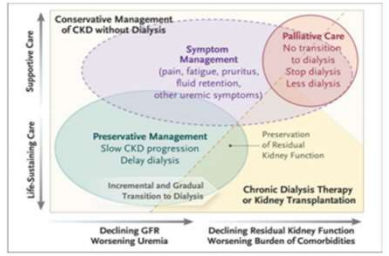
The NEW ENGLAND JOURNAL of MEDICINE

Kamyar Kalantar-Zadeh, M.D., M.P.H., Ph.D., Aaron Wightman, M.D., and Solomon Liao, M.D.

"The 1973 Medicare expansion allowed nearly all Americans with terminal kidney failure access to life-sustaining dialysis. It permitted patients to choose dialysis not just to survive, but also to maintain ***hope***:

hope of continuing valued relationships, hope for rehabilitation, and hope of achieving life goals and pursuits."

"Despite its flaws and burdens, dialysis prolongs life for many people — people who ***choose*** to start or continue this therapy to maintain hope in the face of organ failure."



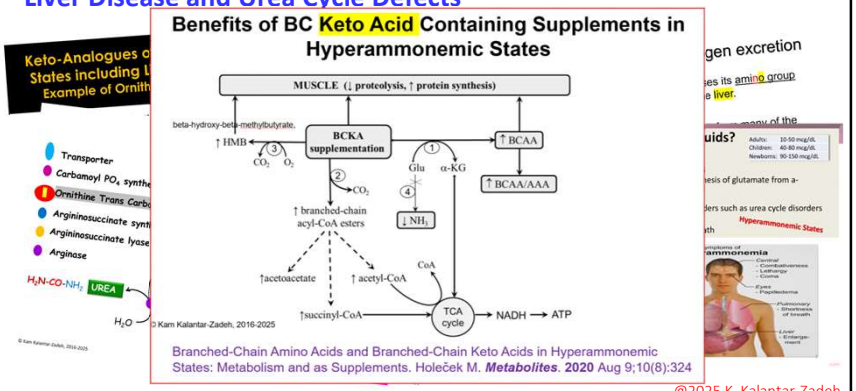
Conceptual Model of the Conservative Management of Advanced CKD

What are the indications for keto-analogues use?

LPD: Low protein Diet, VLDP: Very low Protein Diet

1. LPD in CKD patients (at any stage) with (or at risk of) **Malnutrition** or **Protein-Energy Wasting** (PEW)
2. VLPD in **advanced CKD** GFR <25% (very low kidney function, VLKF) *[currently the main indication of the Fresenius Kabi product]*
3. LPD in **CKD 3-5** <50% (Low Kidney Function, LKF) or transplanted patients with LKF
4. LPD at any CKD stage but with **"heavy" proteinuria** >1g/g
5. LPD in HD and PD patients (ESRD) with **residual renal function** (RRF) for **incremental dialysis** to prolong RRF and lower dialysis dose/frequency
6. Vegan Diet (VLPD or LPD), making vegan diet safer for CKD [and for non-CKD but with **muscle-building** puposes?]
7. **Liver disease** with hyperammonemia states: cirrhosis, urea cycle defects, (not nephrology)

Keto-Analogues of Amino-Acids for Hyperammonemic States, Liver Disease and Urea Cycle Defects



Branched-Chain Amino Acids and Branched-Chain Keto Acids in Hyperammonemic States: Metabolism and as Supplements. Holeček M. ***Metabolites***. **2020** Aug 9;10(8):324

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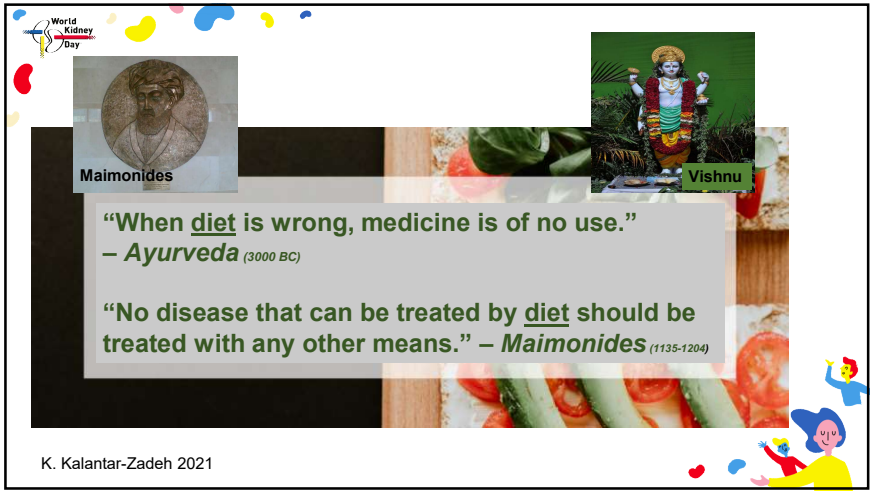
Combing pharmacotherapy and Keto-acid supplemented diet



K. Kalantar-Zadeh 2021

Conclusions: How Can Keto-analogues Help in the New Era of CKD Therapy

- A multi-modal strategy including appropriate nutrition with needed amino-acids but lowest nitrogen load is needed to mitigate the effect of uremic toxins and prevent and correct Protein-Energy Wasting (PEW), Sarcopenia, and Cachexia.
- The 4 groups of CKD/DKD medications RASSi (ACEi & ARB), SGLT2i, MRA, and GLP1 agonists should be combined with keto-analogue supplemented dietary interventions.
- Low Protein Diet (LPD) of 0.6-0.8 g/kg/day and Very Low Protein Diet (VLPD) <0.5 g/kg/day supplemented with keto-analogue supplementation are safe and effective in CKD across the wide spectrum of CKD including Low Kidney Function (LKF, <50%), Very Low Kidney Function (VLKF, <25%), and proteinuric disease.
- Plant Dominant (PLADO) diets with >50% plant proteins and Vegan diet can be supplemented with keto-analogues.
- When dialysis is needed, incremental dialysis transition (once- to twice-weekly) is the goal with continued (V)LPD supplemented with keto-analogues to preserve Residual Kidney Function Longer.
- Keto-analogues use should not be limited to Very Low Protein Diet but should be offered to wide spectrum of kidney disease in addition to medications.

What are the indications for keto-analogues use?

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Combing pharmacotherapy and Keto-acid supplemented diet

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