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Supplementary Appendix

Nutritional Management of Chronic Kidney Disease

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Supplementary-Appendix-Table S2. Selected controlled trials (with greater than 30 participants) that have examined the effects of low-protein or very low-protein diets (with or without supplementation with ketoacids or amino-acids) on various outcome measures in patients with chronic kidney disease.

Study (Year)	Participants	Dietary Intervention	Outcomes	Follow-Up Time	Results	Comment
Rosman et al (1984)[6,7]	247 pts with CKD 3-5	0.90-0.95 g/kg/day (CKD 3) vs. 0.70-0.80 g/kg/day (CKD 4-5) vs. unrestricted DPI	GFR after 2 or 4 years	4 years	After 2 years significant slowing of CKD progression in LPD, but only in male pts.	4-year renal survival improvement in LPD (60% vs. 30%, $p<0.025$). PKD pts did not respond to LPD.
Ihle et al (1989)[8]	72 pts with CKD 4-5	LPD (0.6 g/kg/day) vs. higher DPI (0.8 g/kg/day)	GFR every 6 mos	18 mos	Stable GFR in LPD vs. loss of GFR in control group ($p<0.05$).	LPD pts lost weight but no change in anthropometric measures or serum albumin.
Lindenau et al (1990)[9]	40 pts with CKD 5 (GFR<15 ml/min/1.73m^2)	LPD with calcium suppl. (n=18) vs. sVLPD (0.4 g/kg) with KA (n=22)	Bone and mineral markers including via bone biopsies	12 mos	Decreased serum phosphorus with sVLPD, improved markers of bone breakdown in bone biopsies in sVLPD group.	CKD progression and other outcomes not assessed.
Williams et al (1991)[10]	95 pts with CKD 4-5	LPD (0.7 g/kg/day) vs. normal diet (DPI 1.02 and 1.14 g/kg/day), and varied phos content	CKD progression rates across 3 groups	18 mos	No differences in the reduction in creatinine clearance, dialysis initiation or mortality among 3 groups.	Minor weight loss in LPD.
Locatelli et al (1991)[11]	456 pts CKD 3-4	LPD (0.78 g/kg/day) vs. normal DPI (0.9 g/kg/day), both DEI>30 Cal/kg/day	*Renal survival* defined as dialysis start or doubling of serum creatinine	2 years	Borderline difference, slightly fewer pts assigned to LPD group reached the endpoint ($p = 0.059$).	Substantial overlap in DPI between 2 groups.
MDRD Sudy 2 Klahr et al (1994)[1]	255 pts with CKD 4-5 (GFR 13-24	LPD (0.6 g/kg/day) vs. sVLPD (0.3 g/kg/day with KA)	CKD progression, blood pressure, proteinuria, nutrition	27 mos	sVLPD group had a marginally slower decline in GFR than LPD group ($P=0.067$). Higher calcium, lower phos,	2 concurrent randomized controlled trials. Serum albumin increased in both

	ml/min/1.73 m^2)			(mean follow -up)	alkaline phosphatase, and PTH levels in sVLPD group.	sVLPD and LPD groups and did not differ between groups.
MDRD Sudy 1 Klahr et al (1994)[1]	585 pts with CKF 3-4 (GFR 25-55 ml/min/1.73m^2)	usual-protein diet (DPI 1.3 g/kg/day) vs. LPD (0.6 g/kg/day)	CKD progression, blood pressure, proteinuria, nutrition	27 mos (mean follow -up)	Projected mean GFR decline at 3 years did not differ significantly between the diet groups. Faster GFR decline in the first 4 mos in the LPD group.	2 concurrent randomized controlled trials. Serum albumin increased in both sVLPD and LPD groups and did not differ between groups.
Montes-Delgado et al (1998)[12]	33 pts with CKD 3-5	LPD vs. LPD suppl. with a low-protein and hypercaloric supplement	Renal function and nutritional status	6 mos	Slower CKD progression in the supplemented group, with better nutritional status and higher adherence.	22 patients completed the full 6-mo study.
Malvy et al (1999)[13]	50 pts with CKD 4-5 (eGFR<20 ml/min/1.73m^2)	sVLPD (0.3 g/kg/day) with KA vs. LPD (0.65 g/kg/day)	3 mo to eGFR >5 ml/min/1.73m^2 or need for dialysis	3 years	SUN, lean body mass and fat mass decreased in sVLPD group.	Randomized trial. No difference in renal survival, sVLDP pts lost 2.7 kg (both fat and lean body mass).
Teplan et al (2001) [14]	105 CKD pts (GFR 22-36 ml/min/1.73m^2)	LPD with KA and EPO vs. LPD without KA (with/without EPO)	CKD progression rate and nutritional measures	3 years	sLPD with KA/EPO showed slower CKD progression and increased leucine, isoleucine, valine and mild decrease in proteinuria ($p<0.01$).	Role of EPO remained unclear.
Prakash et al (2004)[15]	34 CKD pts (mean eGFR 28 ml/min/1.73m^2)	LPD (0.6 g/kg/day) with placebo vs. sVLPD (0.3 g/kg/day with KA)	Changes in GFR and nutritional markers	9 mos	Stable GFR in the sVLPD vs. worsening nutritional measures and faster GFR decline in LPD group.	Prospective, randomized, double-blind, placebo-controlled single center trial.
Brunori et al (2007)[16]	56 non-diabetic pts (>70 yrs old) CKD 5 (GFR 5-7 ml/min/1.73m^2)	sVLPD (DPI: 0.3 g/kg/day, DEI: 35 Cal/kg/d) with KA, vs. dialysis initiation	Survival, hospitalization, and metabolic markers.	Median time 26.5 mos	Similar survival in both groups. Patients assigned to dialysis had a 50% higher degree of hospitalization.	There was a continuous benefit of LPD over time.

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Mircescu et al (2007)[17]	53 non-diabetic CKD 4-5 pts (eGFR<30 ml/min/1.73m^2)	sVLPD (0.3 g/kg/day vegetable proteins) suppl. with KA vs. LPD	Transition to dialysis, eGFR, and laboratory markers	48 weeks	Less dialysis initiation with sVLDP (4% vs. 27%). Stable eGFR in sVLDP group, but decreased eGFR in controls.	Open-label randomized, controlled trial. Higher bicarbonate and lower phos in sVLPD group.
Cianciaruso et al (2008)[18]	423 pts with CKD 4-5	2 different DPI levels 0.55 (n=212) vs. 0.80 g/kg/day (n=211)	CKD progression, and changes in blood and urinary biomarkers.	18 mos	Reduced urinary excretion of urea, sodium, phos in LPD. No differences in phos, albumin, PTH, bicarbonate. No changes in body composition.	Estimated DPI in low vs. high groups were 0.72 vs. 0.92 g/kg/day (p< 0.05). 9 vs 13 pts in LPD vs higher DPI stated dialysis.
Di Iorio et al (2009)[19]	32 CKD pts with proteinuria	VLPD vs. LPD	Changes in urinary protein and AGE.	6 mos	58% more reduction in urinary protein excretion and in serum AGE level in VLPD.	Prospective randomized controlled cross-over trial.
Jiang et al (2009 and 2011)[20,21]	60 new ESRD pts on PD with RKF	LPD vs. sLPD (LPD + ketoacids) vs. HPD	RKF and nutritional markers on PD	12 mos	RKF stable in sLPD group but decreased in the LPD and HPD groups.	No change from baseline on nutritional status in any of the groups during follow-up.
Garneata et al (2016)[22]	207 non-diabetic pts with CKD 4-5 (eGFR <30 ml/min/1.73m^2) and proteinuria <1 g/day	LPD (0.6 g/kg/day) vs. sVLPD (vegetarian VLDL 0.3 g/kg/day with KA)	Dialysis initiation or 50% reduction in initial eGFR	15 months	Adjusted NNT (95% CI) to avoid dialysis was 22.4 (21.5-25.1) for pts with eGFR<30 ml/min/1.73m^2 but decreased to 2.7 (2.6-3.1) for pts with eGFR<20 ml/min/1.73m^2 in ITT analysis.	Correction of metabolic abnormalities occurred only with sVLPD. Compliance to diet was good, with no changes in nutritional measure.

Abbreviations: AA, amino-acid; AGE, advanced glycation end products; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; EPO, recombinant human erythropoietin; EAA: Essential amino-acids; GFR, estimated glomerular filtration rate; HPD, high-protein diet; ITT: intention to treat; KA: ketoacids supplement; LPD, low-protein diet; mos, months; NNT: number needed to treat; PD, peritoneal dialysis; PEW: protein-energy wasting; phos, phosphorus; PKD, polycystic kidney disease; pt: patient; pts: patients; RKF, residual kidney function; sLPD, supplemented low-protein diet; SUN, serum urea nitrogen; sVLPD, supplemented very low-protein diet; VLPD, very low-protein diet.

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