Protein Restriction to prevent the progression of diabetic nephropathy

Date written: September 2004
Final submission: September 2005
Author: Kathy Nicholls

GUIDELINES

a. **A small volume of evidence suggests that all patients with renal involvement from diabetes should restrict protein intake to 0.75g/kg/day (WHO recommended minimum safe daily intake). The expected benefit is modest in comparison with the benefits of good blood pressure (BP) control and angiotensin converting enzyme inhibitor (ACEI) therapy. There is Level I evidence for Type 1 diabetes with microalbuminuria or overt nephropathy. Evidence is lacking in Type 2 diabetes with established diabetic nephropathy.**

Background

Clinicians commonly recommend dietary protein restriction in patients with chronic kidney disease (CKD) of any cause. The general evidence has been reviewed by Johnson (2004). This guideline is restricted to evidence of the effect of protein restriction on the progression of diabetic nephropathy. Studies have generally been marred by small numbers, limited follow-up, compliance problems, failure to adequately assess nutritional impact of protein restriction, publication bias, and overlap between “low” and “high” protein intake groups.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCTs) relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A II receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

Date of search: 16 December 2003.

What is the evidence?

Type 1 diabetes

Raal et al (1994) studied the effects of 0.8 g/kg/day protein restriction over 6 months on Type 1 diabetics with overt proteinuria. Proteinuria decreased and GFR stabilised on this reduction of protein intake to 50% of their previously unrestricted diet (> 1.6 gm/kg/day).

Zeller et al (1991) studied 35 Type 1 diabetics with overt nephropathy: over 37 months, the rate of renal functional decline (iodothalamate clearance) on 0.6 g/kg/day protein intake was 0.0055 mL/sec/month vs 0.0168 mL/sec/month in the control group.

Pedrini et al (1996) reported a meta-analysis of 5 RCTs (n = 108) of low protein diet in both diabetic nephropathy and non-diabetic kidney disease patients. Included in the MDRD study were 40% of patients (see below), but only 3% of these had Type 1 diabetes. The analysis concluded that protein restriction significantly reduced the risk of kidney failure or death (RR 0.67, 95% CI: 0.50–0.89), but it is unclear whether symptoms were simply limited by lower protein intake, delaying the need for dialysis.

While the Modification of Diet in Renal Disease (MDRD1989, follow-up Levey et al 1994) was the largest trial examining dietary protein restriction in the progression of renal disease (n = 840), it has limited relevance because it included few diabetic patients. It failed to demonstrate clear benefit, although further analysis by Klahr et al (1994) suggested some benefit.

Waugh and Robertson (update 2000) for the Cochrane Diabetes Group, meta-analysed 5 trials (4 RCT) of low protein diet in Type 1 diabetes, (Table 1) and concluded that protein restriction is beneficial.

Kasiske et al (1998) pooled 13 RCTs of protein restriction (mean 0.7 g/kg/day vs 1.0 g/kg/day) in both diabetic and non-diabetic kidney disease (only 4 of the 13 entered only diabetics). Total n = 1919. In the diabetic subgroup, protein restriction had greater effect on GFR than in the non-diabetic patients, with dietary protein restriction in diabetics reducing the rate of GFR decline by 5.4 mL/min/yr. However, the confidence intervals on this figure were wide at 0.3–10.5 mL/min/year. No analysis of nutritional impact was attempted.

Type 2 diabetes

There is a little data for low protein diet showing progression in Type 2 diabetics with overt nephropathy.

Permerlalu et al (1993) showed in a randomised crossover trial that moderate protein intake at 0.8 gm/kg/day compared to high protein at 2 gm/kg/day improved GFR and decreased proteinuria.

Parving et al (1998) failed to show a benefit of protein restriction in Type 2 diabetics with overt proteinuria.

What is the evidence in children?

There is no evidence available in diabetic nephropathy.

Summary of the evidence

Three meta-analyses (one Cochrane analysis) support the recommendation of modest protein intake in diabetic nephropathy, to the level of the WHO recommended minimum daily intake of 0.75 g/kg/day. The benefit is quantitatively small in comparison with the effects of blood pressure control and renin-angiotensin system blockade.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: American Diabetes Association: With the onset of overt nephropathy, initiate protein restriction to 0.8 g/kg/day (19% of daily calories), the current adult RDA for protein. Further restriction may be useful in slowing the decline of GFR in these patients. (B)

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

World Health Organisation: WHO recommendations for minimum daily protein intake are 1.1 g/kg/day in infants, decreasing to 0.75 g/kg/day in adolescents.

Australian Paediatric Endocrinology Group (2005): Daily energy intake 15%–20% protein, 50%–55% carbohydrate, 25%–40% fat (< 10% as saturated fat).

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

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Appendices

Table 1 Studies in Cochrane meta-analysis – Protein restriction in Type 1 diabetes

Study	Patients	Mean duration (Months)	Design	Dietary protein/ day	Dietary - other	Proteinuria / Albuminuria	Usual diet (pre-study)	Endpoint Ccr decrease	Endpoint Ccr decrease
								Usual protein diet	**Low protein diet**
Barsotti et al, 1988	8 Type 1, overt nephropathy, renal impairment	11	Before (16 mo) & after	0.3 g/kg	Vegetarian, low phosphate, high carbohydrate, AA & KA supplements	-	> 1.2 g/kg/day protein, unrestricted carbohydrate	1.48 mL/min/mo	0.13 mL/min
Dullaart et al, 1993	31 Type 1 microalbuminuria	2 years	RCT	0.7 g/kg	High carbohydrate	AER (mcg/min) UPD 31–29 Proteinuria (g/day) LPD 36–30	1.1 g/kg/day	122–112 mL/min	131–113 mL/min
Raal et al, 1994	26 Type 1, overt diabetic nephropathy (1/2 taking ACEI)	6	RCT	0.8 g/kg	-	UPD 1.9–2.2 LPD 2.2–1.1 g/day	> 1.6 g/kg/day	66–58 mL/min	50–53 mL/min
Ciavarella et al, 1987	16 Type 1 overt nephropathy Cr < 0.2 Uprotein > 0.5 g/day	4.5	RCT	0.7 g/kg	-	AER (mcg/min) UPD 452–850 LPD 434–205	1.5 g/kg/day	0.9 mL/min/mo	Increased by 3.3 mL/min/mo
Zeller et al, 1991	47 Type 1, Uprotein > 0.5 g/day	35	RCT	0.6 g/kg	-	UPD increase LPD decrease	> 1 g/kg/day	0.014 mL/min/mo	0.005 mL/min/mo

UPD=usual protein diet; LPD=low protein diet RCT=randomised controlled trial

Table 2 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Ciavarella et al, 1987	16	Randomised controlled clinical trial	Outpatient clinic	16 patients with Type 1 diabetes and nephropathy	Low protein diet	Normal protein diet	6	
Dullart et al, 1993	31	Randomised controlled clinical trial	Referral-based diabetic clinic	31 patients with overnight albuminuria, without hypertension	Low protein diet / usual protein diet	Unrestricted protein diet	2 yrs	
Raal et al, 1994	32	Randomised controlled clinical trial	Renal diabetic clinic	26 IDDM patients with proteinuria	Low protein diet	Unrestricted protein diet	6	
Zeller et al, 1991	47	Randomised controlled clinical trial	University clinic	35 patients with IDDM Type 1 diabetes and nephropathy	Low protein/ phosphorus diet	Usual diet	35	

Table 3 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Ciavarella et al, 1987	Not specified	No	No	No	Unclear	0.0
Dullaart et al, 1993	Not specified	No	No	No	Yes	0.0
Raal et al, 1994	Not specified	No	No	No	Unclear	15.4
Zeller et al, 1991	Not specified	No	No	No	No	0.0

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Ciavarella et al. 1987	Albumin excretion rate (µg/min)	205 (212)	850 (288)	-645.00 (95%CI: -833.80, -456.20)
	Blood glucose (mg/dL)	172 (46)	185 (41)	-13.00 (95%CI: -56.34, 30.34)
	Glycosylated Hb (%)	8.7 (1.7)	8.6 (1.4)	0.10 (95%CI: -1.46, 1.66)
	Insulin dose (U/day)	41 (7.5)	41 (9)	0.00 (95%CI: -8.09, 8.09)
	Serum creatinine (mg/dL)	1.26 (0.34)	0.97 (0.32)	0.29 (95%CI: -0.04, 0.62)
	Creatinine clearance (mL/min/1.73m^2)	112 (21)	92 (23)	20.00 (95%CI: -1.63, 41.63)
Dullaart et al. 1992	Serum urea (mM)	4.9 (0.6)	5.7 (0.8)	-0.80 (95%CI: -1.30, -0.30)
	Serum albumin (g/L)	43.3 (1.9)	43.8 (2.5)	-0.50 (95%CI: -2.08, 1.08)
	Urinary urea (mmol/24 hr)	274 (85)	386 (91)	-107.00 (95%CI: -170.01, -43.99)
	Urinary phosphate (mmol/24 hr)	27.1 (8.0)	31.4 (6.7)	-4.30 (95%CI: -9.62, 1.02)
	Urinary sodium (mmol/ 24 hr)	151 (50)	158 (39)	-7.00 (95%CI: -1.49, 1.35)
	Urinary calcium (mmol/24 hr)	4.50 (1.91)	4.57 (2.07)	-0.07 (95%CI: -1.49, 1.35)
	GFR at 2 yrs (mL/min/1.73m^2)	113 (24)	112 (21)	1.00 (95%CI: -15.25, 17.25)
Raal et al. 1994	GFR (mL/min/1.73m^2)	53 (23)	58 (26)	-5.00 (95%CI: -25.51, 15.51)
Zeller et al. 1991	Glycosylated Hb (%)	7.8 (0.89)	8.0 (1.55)	-0.20 (95%CI: -1.08, 0.68)
	Mean arterial BP (mmHg)	102.3 (5.37)	105.5 (3.49)	-3.20 (95%CI: -6.14, -0.26)