Specific management of IgA nephropathy: role of fish oil

Date written: July 2005
Final submission: September 2005
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GUIDELINES

Early and prolonged treatment with fish oil may retard the rate of decline in renal function in adults with progressive IgA nephropathy. (Level I evidence, conflicting)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **There is currently insufficient data to confirm the efficacy of fish oil supplementation in adults with IgA nephropathy.**
- **However, in patients at risk for progressive renal impairment, some patients will wish to consider fish oil supplements in addition to other relevant supportive strategies. Although the risk of side-effects is low, possible marginal benefits should be weighted against the costs of compliance.**
- **Optimal dosing also remains to be established but most studies have used 1.8 g of EPA and 1.2 g of DHA daily (~12 g of fish oil per day) for at least 2 years. (Level III evidence – one small study, weak effect)**
- **Ongoing therapy *ad infinitum* may provide greater benefits than intermittent therapy. In the Mayo study (Donadio et al 1994), patients who continued taking fish oil were less likely to reach end-stage kidney disease (ESKD) or increase their creatinine by 50% than those who had discontinued fish oil treatment. (Level III evidence – one small study, weak effect)**
- **No data have been published on the utility of fish oil supplements in children.**

Background

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. ESKD is said to develop in 20% of patients after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function (Rekola et al 1991). In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc) there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD.

Deficiencies of essential fatty acids have been detected in IgA nephropathy. Fish oil is rich in long-chain omega-3–polyunsaturated fatty acids, eicosapentanoic acid, and docosahexanoic acid. Repletion of n-3 fatty acids is thought to lead to the production of less potent prostaglandins and leukotrienes than those produced through the n-6 fatty acid substrate, arachidonic acid (Donadio 2000). N-3 fatty acids can also suppress inflammatory and/or immunological responses through eicosanoid-independent mechanisms. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of fish oil supplementation on renal functional decline in IgA nephropathy.

Search strategy

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for fish oil. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 17 September 2004.

What is the evidence?

Three prospective randomised controlled trials (RCTs) have been published:

- Pettersson et al (1994) reported a short-term prospective, randomised study in 32 patients with non-nephrotic proteinuria and normal- to moderately-impaired renal function. Fifteen patients were assigned to fish oil with a high percentage of [omega]-3-polyunsaturated fatty acids and 17 to corn oil. By 6 months, fish oil administration resulted in a slight but significant reduction in creatinine clearance (63–59 mL/min), whereas no change occurred in the control group. The proteinuria remained unchanged.

- Bennett et al (1989) published a 2-year prospective trial in 37 patients with normal- to severely-impaired renal function, randomly allocated to receive either fish oil or supportive treatment for 2 years. At the end of the trial, the glomerular filtration rate (GFR) in 17 treated patients declined from 80–57 mL/min, and in 20 untreated patients, it went from 76–55 mL/min. There was also no significant effect on proteinuria.

- Collaborators with the Mayo clinic performed a multi-centre, placebo-controlled, randomised trial in 106 patients with normal- to moderately-impaired renal function, and nephrotic range proteinuria. Fifty-five patients were treated with 12 g of fish oil daily and 51 controls received olive oil placebo (Donadio et al 1994). Six per cent in the fish oil group and 33% in the placebo group experienced an increase of 50% or more in the baseline serum creatinine at 2 years (P = 0.002). The cumulative percentage of patients who died or developed ESKD after 4 years was 10% in the fish oil group and 40% in the placebo group (P = 0.006). Fish oil also slowed the rate of decline in GFR. There was no effect on the level of proteinuria. In a follow-up study of the original 106 patients, now beyond 6 years, progression to ESKD remained

substantially lower in the fish oil group and those who continued fish oil therapy (Donadio et al 2001). However, results were not improved by the use of higher doses of fish oil (Donadio et al 1999).

Two meta-analyses (Strippoli et al 2003, Dillon 1997) have been performed, both of which concluded that a clear beneficial effect could not be demonstrated. When all studies were combined, the mean effect was not statistically significant, although the probability of at least a minor beneficial effect was 75%. Mixed-effects regression suggested that fish oil therapy may have been slightly more effective among individuals with greater levels of proteinuria.

No data have been published on the use of fish oil supplements in children with IgA nephropathy.

Summary of the evidence

Some, but not all studies, have shown that early and prolonged treatment with fish oil may retard the rate of decline in renal function in patients with progressive IgA nephropathy. However, fish oil has no significant effect on proteinuria in patients with IgA nephropathy. Overall, there is currently insufficient data to confirm the efficacy of fish oil supplementation in patients with IgA nephropathy.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: In patients with a slow progressive decline in creatinine clearance (less than 70 mL/min), fish oil should be given (Nolin & Courteau 1999).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

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Rekola S, Bergstrand A, Bucht H. Deterioration of GFR in IgA nephropathy as measured by 51Cr-EDTA clearance. Kidney Int 1991; 40: 1050–4.

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Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Bennet et al, 1989	37	Randomised controlled clinical trial	Hospital, Melbourne	37 patients with biopsy-proven mesangial IgA nephropathy	Eicosapentanoic acid (EPA) 10 g/d	No treatment	24	Group A serum Cr > 0.12 mmol/L; Group B serum Cr < 0.12 mmol/L
Donadio et al, 2001	73	Randomised controlled clinical trial	14 centres of the Mayo Nephrology Collaborative Group	73 patients with severe IgA nephropathy	High dose fatty acids (EPA 3.76 g, DHA 2.94 g)	Low dose fatty acids (EPA 1.88 g, DHA 1.47 g)	24	
Donadio et al, 1994	106	Randomised controlled clinical trial	21 centres making up the Mayo Nephrology Collaborative Group, US	106 patients with IgA nephropathy who had persistent proteinuria	Fish oil 12 g/d	Placebo olive oil 12 g/d	36	
Pettersson et al, 1994	34	Randomised controlled clinical trial	University hospital, Sweden	34 adult patients with biopsy-proven IgA nephropathy	Fish oil (55% eicosapentanoic and 30% docosahexanoic acid)	Placebo corn oil	6	

Table 2 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)		
Bennet et al, 1989	Not specified	No	No	No	Unclear	0.0
Donadio et al, 2001	not specified	No	No	No	No	42.5
Donadio et al, 1994	Not specified	Yes	Yes	Yes	No	29.2
Pettersson et al, 1994	Not specified	Yes	Yes	Yes	No	5.9

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Bennet et al, 1989	Group A serum Cr (nmol/L) compared to baseline	0.19 (0.14)	0.22 (0.08)	-0.03 (95%CI: -0.14, 0.08)
	Group B serum Cr (nmol/L) compared to baseline	0.07 (0.20)	0.01 (0.03)	0.06 (95%CI: -0.07, 0.19)
Donadio et al, 2001	SBP (mmHg) at 2 yrs	136 (13)	136 (17)	0.00 (95%CI: -8.04, 8.04)
	DBP (mmHg) at 2 yrs	83 (8)	81 (8.9)	2.00 (95%CI: -2.51, 6.51)
	Cholesterol (mg/dL)	212 (57)	206 (50)	6.00 (95%CI: -22.69, 34.69)
Donadio et al, 1994	Change in SBP (mmHg) In hypertensive patients at 1 yr	-11 (19)	-9 (21)	-2.00 (95%CI: -13.02, 9.02)
	Change in SBP (mmHg) in normotensive patients at 1 yr	4 (14)	-1 (15)	5.00 (95%CI: -4.79, 14.79)
	Change in DBP (mmHg) in hypertensive patients at 1 yr	-6 (9)	-3 (11)	-3.00 (95%CI: -8.56, 2.56)
	Change in DBP (mmHg) in normotensive patients at 1 yr	-1 (9)	0.1 (8)	-1.10 (95%CI: -6.81, 4.61)
Pettersson et al, 1994	SBP (mmHg) at 6 mo	136 (15)	142 (19)	-6.00 (95%CI: -17.80, 5.80)
	SDP (mmHg) at 6 mo	81 (7)	82 (9)	-1.00 (95%CI: -6.55, 4.55)
	Mean increase in body weight at 6 mo (kg)	2.1 (2.7)	0.2 (2.9)	1.90 (95%CI: -0.04, 3.84)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Bennet et al, 1989	ESRD	2/17	2/20	1.18 (95%CI: 0.18, 7.48)	0.02 (95%CI: -0.18, 0.22)
Donadio et al, 2001	Death	0/36	0/37	Not estimable	0.00 (95%CI: -0.05, 0.05)
	Adverse events	4/36	5/37	0.81 (95%CI: 0.24, 2.82)	-0.02 (95%CI: -0.17, 0.13)
	Diverticulitis	0/36	1/37	0.34 (95%CI: 0.01, 8.14)	-0.03 (95%CI: -0.10, 0.05)
	Hyperkalaemia	0/36	1/37	0.34 (95%CI: 0.01, 8.14)	-0.03 (95%CI: -0.10, 0.05)
	ESRD	8/36	10/37	0.82 (95%CI: 0.37, 1.85)	-0.05 (95%CI: -0.25, 0.15)
Donadio et al, 1994	Death, repeated dialysis, transplant	14/55	5/51	2.60 (95%CI: 1.01, 6.70)	0.16 (95%CI: 0.02, 0.30)
	Increase of ≥ 50% serum Cr	3/55	14/51	0.20 (95%CI: 0.06, 0.65)	-0.22 (95%CI: -0.36, -0.08)
	ESRD	4/55	14/51	0.26 (95%CI: 0.09, 0.75)	-0.20 (95%CI: -0.34, -0.06)
Pettersson et al, 1994	No change in GFR	2/15	2/17	1.13 (95%CI: 0.18, 7.09)	0.02 (95%CI: -0.21, 0.25)
	Improved ^{51}Cr-EDTA clearance	2/15	6/17	0.38 (95%CI: 0.09, 1.60)	-0.22 (95%CI: -0.50, 0.07)