Nutritional interventions for the prevention of bone disease in kidney transplant recipients

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GUIDELINES

Kidney transplant recipients should be advised to take a vitamin D (or analogue) supplement at a dose of at least 0.25 μg daily. (Level I and II)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **The treating physician should determine the dose of vitamin D and the necessity of other treatments for minimizing bone mineral density loss, on the basis of available evidence.**
- **A diet containing adequate calcium-rich foods to meet the NHMRC recommended dietary intake (RDI) for calcium[1] should be encouraged as follows:**

Age	RDI men	RDI women
19–30 years	1000 mg/day	1000 mg/day
31–50 years	1000 mg/day	1000 mg/day
51–70 years	1000 mg/day	1300 mg/day
>70 years	1300 mg/day	1300 mg/day

- **If the diet does not provide adequate calcium, a calcium supplement should be recommended.**
- **The diet should meet the levels of adequate intake (AI) for dietary vitamin D that are recommended for the general population, which assume minimal or no sun exposure*:[1]**

19–50 years	5 μg
31–50 years	5 μg
51–70 years	10 μg
Over 70 years	15 μg

*Kidney transplant recipients may be advised to limit sun exposure.[2] The major dietary sources of vitamin D are fatty fish (salmon, herring and mackerel), liver, eggs and fortified foods, such as margarine and some varieties of low-fat milk. There are limited data on vitamin D content of local foods.[1]

BACKGROUND

A rapid decline in bone mineral density occurs in the early post-transplant period.[3,4] Though the rate of bone loss may decelerate once only around 3 years post-transplant, bone mineral density remains below normal.[5]

The risk of bone fractures among kidney transplant recipients is four times that among the general population.[6]

At the time of transplantation, there are usually already significant abnormalities of bone remodelling related to chronic kidney disease.[7] Reduced calcium absorption due to prednisone,[8] hyperparathyroidism[9] and abnormal vitamin D metabolism[10] are among the factors contributing to the further weakening of bones and the risk of bone disease post-transplantation. There is an increased risk of bone loss among females, particularly post-menopausal.[11]

This review set out to explore and collate the evidence to support the use of particular nutrition interventions for the prevention and management of bone disease in kidney transplant recipients, based on the best evidence up to and including September 2006.

SEARCH STRATEGY

Relevant reviews and studies were obtained from the sources below and reference lists of nephrology textbooks, review articles and relevant trials were also used to locate studies. Searches were limited to human studies on adult transplant recipients and to studies published in English.

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for both bone disease and dietary interventions MEDLINE – 1966 to week 1, September 2006; EMBASE – 1980 to week 1, September 2006; the Cochrane Renal Group Specialised Register of Randomised Controlled Trials.

Date of searches: 22 September 2006.

WHAT IS THE EVIDENCE?

There are no published studies examining the potential role of diet per se in preventing and treating bone disease in

adult kidney transplant recipients. However, a systematic review of randomized controlled trials, completed in 2005 (updated in 2007) examined the effect of vitamin D and/or calcium supplementation on bone disease in this population.[12]

Treatment with vitamin D *versus* no treatment

The meta-analysis of two randomized controlled trials (46 patients) comparing treatment with 0.5 μg/d oral calcitriol with no treatment revealed a significantly favourable effect on bone mineral density at the lumbar spine and the neck of femur. However, the authors of the systematic review note that clinical significance of this is uncertain due to the lack of validation in bone densitometry in chronic kidney disease.[12]

In a randomized controlled study (40 patients), El-Agroudy *et al.* showed that treatment with vitamin D (or analogue) compared with placebo is *not* associated with hypercalcaemia or increased plasma creatinine level.[13]

The results of individual randomized controlled trials suggest that treatment with either vitamin D, calcitonin *or* bisphonate alone does not reduce fracture risk after kidney transplantation, however, the meta-analysis of all such trials combined (24 trials, 1299 patients) shows that treatment with either of these agents *does* reduce the risk of fracture in kidney transplant recipients.[12]

Treatment with vitamin D (or analogue) and calcium *versus* no treatment

Palmer *et al.*[12] conducted a meta-analysis of two randomized controlled trials, comparing treatment with both vitamin D and calcium *versus* no treatment on bone mineral density at the lumbar spine and femoral neck. The first trial compared treatment with 1000 mg calcium lactogluconate and 0.25 μg 1-alpha-hydroxyvitamin D with no treatment, over a 6 month period.[14] The second trial compared treatment with 3000 mg calcium carbonate and 40 μg 25-hydroxvitamin D3 with no treatment, over a 12 month period.[15] The meta-analysis of the results shows a significant difference between treatment and placebo groups favouring active treatment.

Torres *et al.*[16] in a randomized controlled study (86 patients) showed that treatment with vitamin D (0.5 μg calcitriol alternate days) *and* calcium (1.5 g/d calcium lactogluconate) does *not* increase the risk of hypercalcaemia nor increase plasma creatinine level compared with treatment with calcium alone.

In their meta-analysis, Palmer *et al.* concluded that treatment with vitamin D or analogue *and* calcium compared with placebo is *not* associated with a statistically significant difference in risk of fracture at any site, acute graft rejection, presence of low bone turnover on bone histomorphometry, gastro-oesophageal disorder or graft loss or increased plasma creatinine level. However, the authors caution that the applicability of these findings is reduced because the reporting of each outcome was limited to one or two trials in the meta-analysis.[12]

Treatment with calcium

There is little evidence that calcium supplementation alone is effective in maintaining bone mineral density or reducing bone fracture risk.

In a double-blind randomized controlled trial, Torres *et al.* studied the effects of daily low dose (1500 mg) calcium supplementation in the first year post-transplant compared with a combination of this treatment with vitamin D supplementation (0.5 μg every other day) for the first 3 months post-transplant. They found that the combination treatment was more effective at preserving bone mineral density at the hip.[16]

A similar finding was reported by Uğur *et al.*[17] who, in a randomized trial, compared four treatments: daily supplementation of 3 g calcium and 0.5 μg calcitriol; 3 g calcium carbonate with 0.5 μg calcitriol and nasal calcitonin; 3 g calcium alone; and no treatment. They showed that calcitriol with daily calcium supplementation abates the usual decrease in bone mineral density, however, they were unable to show a significant improvement in bone mineral density, possibly due to small sample size and short duration of follow-up.

SUMMARY OF THE EVIDENCE

There are no published studies examining the potential role of diet per se in preventing and treating bone disease in adult kidney transplant recipients.

Meta-analysis of randomized controlled show that any intervention (bisphopshate, vitamin D sterol or calcitonin) for bone disease in kidney transplant recipients reduces the risk of fracture in this population. These agents have also been shown to provide a statistically significant improvement in bone mineral density when given after transplantation, however, the clinical significance of this difference remains uncertain.

There is little evidence that calcium supplementation alone is effective in maintaining bone mineral density or reducing bone fracture risk.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative:[18] No guideline on nutritional management including vitamin D or calcium.

Recommendations regarding monitoring of serum calcium, phosphorus and intact parathyroid hormone.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines:[19] Recommendations include: 0.25–0.5 μg/day calcitriol or 600 IU cholecalciferol; 1000 mg/day calcium (1500 mg post-menopause); treat persistent severe hypophosphatemia and hypomagnesaemia; cessation of smoking; and initiation of exercise.

International Guidelines:[20] Minimum calcium intake 1500 mg. Minimum vitamin D intake 400–1000 IU.

IMPLEMENTATION AND AUDIT

No recommendations.

SUGGESTIONS FOR FUTURE RESEARCH

The studies to date have only looked at particular supplements rather than overall diet. They have not been able to demonstrate the impact of treatments on fracture risk due to their small sample sizes and short duration. The Cochrane reviewers suggest that a randomized trial with a power of 80% would require 266 enrolments.

Well-designed, randomized controlled trials in the kidney transplant population are required to determine the effect of diet (including dietary calcium and vitamin D), as well as lifestyle changes (such as increased exercise and smoking cessation) on bone mineral density and fracture risk.

CONFLICT OF INTEREST

All the above authors have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

Table A1 Characteristics of included studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up	Comments
Palmer et al. 2005	23 trials 1209 patients	Systematic review		Kidney transplant recipients of any age, receiving any immunosuppression regimen. Recipients of any other transplant were excluded.	Bisphosphonates, vitamin D or derivatives, calcitonin and gonadal replacement, fluoride, anabolic steroids; calcium supplementation could also be taken			No individual intervention has been shown in RCTs to reduce fracture risk after kidney transplantation. Meta analysis of all available trials combined, shows that bisphosphonate, vitamin D sterol, or calcitonin does reduce the risk of fracture. These agents also provide a significant improvement in bone mineral density when given after transplantation (the clinical significance of this is uncertain). Bisphosphonates have greater efficacy to preserve bone mineral density than vitamin D sterols in head-to-head trials.
El-Agroudy et al. 2003	40	Randomized clinical trial	Egypt	Live-donor renal transplant recipients, greater than 20 years, no diabetes, no steroids before transplantation, haemodialysis for not more than 2 years	Alfacalcidol 0.5 mg Calcium carbonate 500 mg	No treatment	12 months	Treatment with vitamin D (or analogue) compared with placebo is not associated with hypercalcaemia or increased plasma creatinine level.
Torres 2004	90	Randomized controlled clinical trial	Spain	86 kidney transplant recipients	Calcitriol	Placebo	3 months	Treatment with calcitriol (alternate days) and calcium lactogluconate does not increase the risk of hypercalcaemia nor increase plasma creatinine level compared with treatment with calcium alone.
Ugur 2000	45	Randomized controlled clinical trial	Turkey	45 kidney transplant recipients	Group 1: calcium and calcitriol Group 2: calcium, calcitriol, nasal calcitonin Group 3: calcium only	No treatment	12 months	They showed that calcitriol with daily calcium supplementation abates the usual decrease in bone mineral density, however they were unable to show a significant improvement in bone mineral density, possibly due to small sample size and short duration of follow-up.

Table A2 Quality of randomized trials

Study ID (author, year)	Method of allocation concealment*	Blinding			Intention-to-treat analysis†	Loss to follow up (%)
		Participants	Investigators	Outcome assessors		
El-Agroudy 2003	Unclear	No	Yes	Not stated	No	0
Torres 2004	Sealed envelope with the lowest available number	Yes	Yes	Yes	No	4.4
Ugur 2000	Not specified	No	No	No	unclear	0.0

*Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.
†Choose between: yes; no; unclear.

Table A3 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]
Torres 2004	Symptomatic fracture	0/45	0/41	Not estimable	0.00 (95% CI: −0.04, 0.04)

Table A4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean (SD))	Control group (mean (SD))	Difference in means [95% CI]
Torres 2004	Creatinine (mg/dL) at 12 months	1.37 (0.3)	1.3 (0.4)	0.07 (95% CI: −0.08, 0.22)
	Proteinuria (g/day) at 12 months	0.1 (0.5)	0.1 (0.2)	0.00 (95% CI: −0.16, 0.16)
	Calcium (mg/dL) at 12 months	9.95 (0.6)	9.8 (0.5)	0.15 (95% CI: −0.08, 0.38)
	Phosphate (mg/dL) at 12 months	3.7 (0.6)	3.8 (0.7)	−0.10 (95% CI: −0.38, 0.18)
	PTH (pg/mL) at 12 months	67.3 (33.7)	82.6 (37.0)	−15.30 (95% CI: −30.31, −0.29)
	Lumbar spine (g/cm^2) at 12 months	0.99 (0.10)	0.93 (0.11)	0.096 (95% CI: 0.01, 0.11)
	Femoral neck (g/cm^2) at 12 months	0.82 (0.11)	0.74 (0.10)	0.08 (95% CI: 0.03, 0.13)
	Trochanteric region (g/cm^2) at 12 months	0.68 (0.12)	0.63 (0.12)	0.05 (95% CI: −0.01, 0.11)
	Intertrochanteric region (g/cm^2) at 12 months	1.07 (0.12)	1.01 (0.13)	0.06 (95% CI: 0.00, 0.12)
	Ward's triangle (g/cm^2) at 12 months	0.64 (0.15)	0.54 (0.14)	0.10 (95% CI: 0.03, 0.17)
	Total hip (g/cm^2) at 12 months	0.91 (0.12)	0.85 (0.12)	0.09 (95% CI: 0.03, 0.15)
El-Agroudy	Creatinine (mg/dL) at 12 months	1.4 (0.4)	1.5 (0.4)	P (between groups) = 0.18
	Calcium (mg/dL) at 12 months	9.9 (0.4)	9.3 (0.3)	P (between groups) = 0.001
	Phosphate (mg/dL) at 12 months	3.3 (0.6)	3.5 (0.4)	P (between groups) = 0.36
	Serum intact PTH (pmol/mL)	2.8 (1.7)	4.8 (2.7)	P (between groups) = 0.04
	Serum osteoclacin (ng/mL)	12.5 (6.6)	16.5 (13)	P (between groups) = 0.03
	Lumbar spine (g/cm^2) at 12 months	1.2 (0.11)	1.1 (0.30)	P (between groups) = 0.44
	Femoral neck (g/cm^2) at 12 months	1.0 (0.02)	0.91 (0.1)	P (between groups) = 0.26
	Forearm (g/cm^2) at 12 months	0.9 (0.14)	0.7 (0.04)	P (between groups) = 0.03