Biochemical Targets

CARMEL HAWLEY *(Woolloongabba, Queensland)*
GRAHAME ELDER *(Westmead, New South Wales)*

Calcium

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Author: Carmel Hawley

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **In Stage 5 kidney disease, predialysis albumin-corrected serum calcium should be kept within the normal laboratory reference range, preferably towards the lower end (2.1–2.4 mmol/L) provided that keeping serum calcium at this level does not worsen hyperparathyroidism. (Opinion)**
- **In Stage 3 and 4 kidney disease, serum calcium should be kept within the normal laboratory reference range. (Opinion)**
- **A predialysis blood sample should be used. (Level III evidence)**

Background

Parameters of bone mineral metabolism have been associated with metabolic bone disease seen in patients with renal impairment. In addition, evidence is emerging that these parameters may have a role in the high mortality and in particular, cardiovascular mortality seen in patients with kidney disease.

We set out to explore whether there is an association between serum calcium and all-cause mortality and cardiovascular mortality in particular while giving consideration to the well-established link between hypocalcaemia and worsening hyperparathyroidism.

Search strategy

Databases searched: MeSH terms and text words for kidney dialysis were combined with MeSH terms and text words for serum calcium. This search was carried out in Medline (1966 to April Week 3, 2005). The Cochrane Renal Group Trials Register was also searched for calcium trials not indexed in Medline.

Date of searches: 3 March 2004. A further Medline search was carried out for the period 1 Feb 2004 to 30 Apr 2005.

What is the evidence?

There are no available randomised controlled trials (RCTs)
– all data is at level III or lower.
However, the literature to date suggests a moderate to strong association between serum calcium and all-cause mortality, although this effect is not demonstrated consistently in all studies. There is also an association between serum calcium and all-cause hospitalisation and cardiovascular mortality.

Summary of the evidence

Is there a relationship between indices of bone mineral metabolism and extra-skeletal outcomes?

All-cause mortality
There have been up to 6 key observational studies exploring this. Of these, Block et al (2004) & Young et al (2005) showed a moderately strong association between increasing serum calcium and all-cause mortality. The data to date thus supports the association between a higher serum calcium and mortality and the earlier studies are likely to have been subject to a type 2 error or to problems relating to confounding and small sample size.

The effect of a low serum calcium < 2.20 mmol/L is less certain. Importantly, Lowrie and Lew (1990) suggested that hypocalcaemia was independently associated with mortality and Foley et al (1996) showed that a serum calcium < 2.20 mmol/L (8.8 mg/dL) was associated with increased mortality. These data have recently been challenged by data from Block et al (2004) & Young et al (2005). Block et al (2004) showed that low serum calcium < 1.96 mmol/L (8.0 mg/dL) was associated with a lower relative risk of all-cause mortality compared to the referent range of 2.25–2.4 mmol/L and a similar result was demonstrated by Young et al (2005) for serum calcium < 1.96 mmol/L (< 7.8 mg/dL).

The unexpected finding of a decreased mortality in patients with serum calcium in the low normal range and even below the normal range is of interest but needs to be interpreted with caution. The reason for hypocalcaemia being not an uncommon finding in these studies is not readily explained. Thus, the data relating to the effect of hypocalcaemia is currently controversial and requires further investigation. We need to be cautious: hypocalcaemia is universally accepted as a major factor in the pathogaesis of secondary hyperparathyroidism. His currently not advisable to recommend allowing patients to become hypocalcaemic until further data becomes available.

Disease-specific mortality

Only one large observational study has demonstrated an association between cardiovascular mortality and serum calcium, with mortality increasing with increasing serum calcium (Young et al 2005).

Additional summary comments

Metastatic calcification
Hypercalcaemia induced by calcium and calcitriol therapy is associated with risks of metastatic calcification (Ginsburg et al 1973, Gonella et al 1985) and may aggravate cardiac morbidity and mortality by causing calcification of advanced plaques and valvular calcification (Kramer et al 1986, Lowrie et al 1992, Maher and Curtis 1985, Nishimura et al 1992).

Dialysate calcium concentration
The ideal dialysate calcium is controversial. Recently, Young et al (2005) (DOPPS) found an independent association between dialysate calcium and mortality (RR 1.13 per 0.25 mmol/L (1 mEq/L) increase in dialysate calcium, P = 0.01).

Predialysis blood sampling
In one prospective cohort study of 47 randomly selected haemodialysis patients, change in serum ionised calcium during dialysis was dependent on the concentration difference between the serum and dialysate ionised calcium. (Saha et al 1996).

Difficulty achieving targets
The difficulty achieving serum calcium targets has been discussed in the literature. In particular, Young et al (2004) explored this with DOPPS data. In their study, only 40.5 % and 42.5% of patients achieved K/DOQI guidelines for serum calcium (2.1–2.4 mmol/L).

Relevant studies

(Note: where the details of the trial design have been described in the "Recommended target range for serum phosphate" only the details pertaining to the data relating to calcium will be given in this guideline.)

Lowrie and Lew (1990) suggested hypocalcaemia may be an independent risk factor for mortality in their logistic regression analysis of over 12,000 haemodialysis patients. This effect was particularly marked when ionised calcium was considered and persisted after adjusting for baseline demographics, diabetes, type of renal disease and a number of laboratory variables.

Based on a prospective study commenced in 1982 of 433 dialysis patients, Foley et al (1996) reported that chronic hypocalcaemia was closely associated with mortality in both haemodialysis and CAPD patients (RR 2.1, P = 0.006) for a mean calcium level < 2.2 mmol/L (8.8 mg/dl) and was also associated with de novo ischemic heart disease (IHD) (RR 5.23, P < 0.001), cardiac failure (RR 2.64, p < 0.001), recurrent ischaemic heart disease (IHD) and CCF. Patients with mean serum calcium < 2.2 mmol/L (8.8 mg/dl) had a RR of death 2.9 times that of patients with values > 2.2

mmol/L (P < 0.001). Conclusions were similar for albumin-adjusted calcium. The RR increased progressively from 5.1 for albumin-adjusted calcium < 2.1 mmol/L (< 8.2 mg/dL) (P = 0.08) to 7.4 for calcium < 1.9 mmol/L (7.6 mg/dL) (P = 0.04). Since this study was designed in the early 1980s, the impact of inadequate dialysis and inadequate dialysate calcium may have contributed to the outcome.

A comprehensive study addressing the influence of calcium levels on mortality by Block et al (1998)-using data from the US Dialysis Morbidity and Mortality Study (DMMS) database on 2669 haemodialysis patients chosen randomly from 550 dialysis units-demonstrated no correlation was found between serum calcium and relative risk of death.

Block (1998) demonstrated no link between mortality and serum calcium as outlined below. Relative risk (RR) of mortality by serum calcium quintiles (N = 2669) was:

Serum Ca	
0.9–2.2 mmol/L (3.7–8.6 mg/dL)	RR 0.96
2.2–2.3 mmol/L (8.7–9.1 mg/dL)	RR 1.05
2.3–2.4 mmol/L (9.2–9.5 mg/dL)	RR 1.00
2.4–2.5 mmol/L (9.6–10.1 mg/dL)	RR 0.95
2.6–4.4 mmol/L (10.2–17.5 mg/dL)	RR 0.91

However, a larger study (Block et al 2004) with more robust analytical methods has shown the link between serum calcium and mortality and in particular, cardiovascular mortality. In this study, it was demonstrated that there was an independent association between serum calcium concentrations and an increased relative risk of death across the spectrum of serum calcium. This showed that albumin-corrected serum calcium down to 1.96 mmol/L (< 8 mg/dL) was associated with a lower relative risk of mortality. Of interest, there was a relatively large proportion (17.6%) of patients with hypocalcaemia in this study, which is unexplained in the publication. In addition, analyses were done examining the effect of various levels of serum calcium on fixed ranges of serum phosphate, demonstrating that higher serum calcium was associated with a higher RR of mortality at all categories of serum phosphate as in the following table:

Calcium & Phosphate mortality relationship : for Serum phosphate band mg/dl (mmol/L)	RR of death with - Ca (albumin-corrected)
4–5 (1.28–1.6)	1.25
5–6 (1.61–1.92)	1.20
6–7 (1.93–2.24)	1.19
7–8 (2.25–2.56)	1.18

Young et al 2005 also found that increasing serum calcium was independently associated with increased mortality (RR 1.10 per 0.25 mmol/L (1 mg/dL) ,P < 0.0001). In addition, serum calcium was also shown to be independently predictive of cardiovascular mortality (RR 1.14, P < 0.0001).

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: In CKD patients (Stages 3 and 4): The serum levels of corrected total calcium should be maintained within the "normal" range for the laboratory used. (Evidence)

In CKD patients with kidney failure (Stage 5): Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4–9.5 mg/dL [2.10–2.37 mmol/L]). (Opinion)

British Renal Association: Recommended standards for haemodialysis (5.38) and peritoneal dialysis (6.12): total calcium within normal limits for local laboratory corrected for serum albumin or normal ionised calcium where available.

Chronic renal failure (predialysis) (9.10): 2.2–2.7 mmol/L (corrected for serum albumin) concentration, or normal ionised calcium where available.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

INTERNATIONAL GUIDELINES: No recommendation.

Implementation and audit

Audit of adjusted serum calcium and dialysate calcium through ANZDATA registry should be considered in conjunction with PTH, phosphate and calcium x phosphate product.

Exploring the prevalence of overt hypocalcaemia in the Australian and New Zealand dialysis population.

Suggestions for future research

Is an adjusted calcium level outside the recommended range associated with excess morbidity or mortality in Australian haemodialysis or CAPD patients?

A randomised controlled trial with the study factor of different target ranges of adjusted serum calcium and exploring outcomes, including morbidity and mortality and hyperparathyroid status.

Studies exploring optimal dialysate calcium are recommended.

Cohort study exploring serum calcium as a predictor of mortality in the peritoneal dialysis population is recommended.

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