

Highlighted Abstracts for Appendix V – Importance of Balancing Ca with Mg . . .

The Ca:Mg ratio in US diets is increasing – see Figs. 5a, 5b & 6

Rosanoff, A. (2010). "Rising Ca:Mg intake ratio from food in USA Adults: a concern?" *Magnes Res* **23**(4): 181-193. ([See Full Paper](#))

USDA food surveys from 1977 through 2007-8 show a rising food Ca:Mg ratio for all USA adult age-gender groups. **Food Ca:Mg intake ratios rose from 2.3-2.9 in 1977 to 2.9-3.5 in 2007-8.** The % rise in mean Mg intakes compared closely with % rise in mean energy intakes while % rise in mean Ca intakes were substantially higher in all groups, suggesting **the rising Ca:Mg comes from higher Ca intakes via food selections, rising food Ca contents or both.** Original intake data from these surveys need to be accessed to calculate each individual's Ca:Mg for statistical assessment of this ratio rise. Ca:Mg rose from largely below 3.0 in 1994-5 to generally above or approaching 3.0 after 2000, coinciding with a sharp **2% rise in type 2 diabetes incidence and prevalence in the USA** population and a 1994-2005 rise in **colorectal cancer incidence** among young white, non-Hispanic adult men and women in the USA. The intracellular Ca activation response to low Mg is discussed as a possible mechanism linking metabolic and inflammatory syndromes with low dietary Mg and rising dietary Ca:Mg ratio. Adequacy of both Ca and Mg as well as the Ca:Mg ratio are important in assessing study outcomes. **Health consequences should be considered for the USA's 64-67% adults not meeting their Mg requirement from foods, many also consuming below their Ca requirements, and their increasing Ca:Mg ratio from foods.**

Rosanoff, A., et al. (2012). "Suboptimal magnesium status in the United States: are the health consequences underestimated?" *Nutr Rev* **70**(3): 153-164. ([See Full Paper](#))

In comparison with calcium, magnesium is an "orphan nutrient" that has been studied considerably less heavily. **Low magnesium intakes and blood levels have been associated with type 2 diabetes, metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer.** **Almost half (48%) of the US population consumed less than the required amount of magnesium from food in 2005-2006, and the figure was down from 56% in 2001-2002.** **Surveys conducted over 30 years indicate rising calcium-to-magnesium food-intake ratios among adults and the elderly in the United States, excluding intake from supplements, which favor calcium over magnesium.** The prevalence and incidence of type 2 diabetes in the United States increased sharply **between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0.** Dietary Reference Intakes determined by balance studies may be misleading if subjects have chronic latent magnesium deficiency but are assumed to be healthy. **Cellular magnesium deficit, perhaps involving TRPM6/7 channels, elicits calcium-activated inflammatory cascades independent of injury or pathogens.** Refining the magnesium requirements and understanding how low magnesium status and rising calcium-to-magnesium ratios influence the incidence of type 2 diabetes, metabolic syndrome, osteoporosis, and other inflammation-related disorders are research priorities.

Recent studies show Ca supplementation puts people more at risk of CVD.

Li, K., et al. (2012). "Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg)." *Heart* **98**(12): 920-925.

BACKGROUND: It has been suggested that a higher calcium intake might favourably modify cardiovascular risk factors. However, findings of an ultimately decreased risk of cardiovascular disease (CVD) are limited. Instead, **recent**

evidence warns that taking calcium supplements might increase myocardial infarction (MI) risk. OBJECTIVE: To prospectively evaluate the associations of dietary calcium intake and calcium supplementation with MI and stroke risk and overall CVD mortality. METHODS: Data from 23 980 Heidelberg cohort participants of the European Prospective Investigation into Cancer and Nutrition study, aged 35-64 years and free of major CVD events at recruitment, were analysed. Multivariate Cox regression models were used to estimate HRs and 95% CIs. RESULTS: After an average follow-up time of 11 years, 354 MI and 260 stroke cases and 267 CVD deaths were documented. Compared with the lowest quartile, the third quartile of total dietary and dairy calcium intake had a significantly reduced MI risk, with a HR of 0.69 (95% CI 0.50 to 0.94) and 0.68 (95% CI 0.50 to 0.93), respectively. Associations for stroke risk and CVD mortality were overall null. **In comparison with non-users of any supplements, users of calcium supplements had a statistically significantly increased MI risk (HR=1.86; 95% CI 1.17 to 2.96), which was more pronounced for calcium supplement only users (HR=2.39; 95% CI 1.12 to 5.12).** CONCLUSIONS: Increasing calcium intake from diet might not confer significant cardiovascular benefits, while calcium supplements, which might raise MI risk, should be taken with caution.

Reid, I. R., et al. (2011). "Cardiovascular effects of calcium supplementation." *Osteoporos Int* **22**(6): 1649-1658.

Trials in normal older women and in patients with renal impairment suggest that calcium supplements increase the risk of cardiovascular disease. To further assess their safety, we recently conducted a meta-analysis of trials of calcium supplements, and found a 27-31% increase in risk of myocardial infarction and a 12-20% increase in risk of stroke. These findings are robust because they are based on pre-specified analyses of randomized, placebo-controlled trials and show consistent risk across the trials. The fact that cardiovascular events were not primary endpoints of any of these studies will introduce noise but not bias into the data. A recent re-analysis of the Women's Health Initiative suggests that co-administration of vitamin D with calcium does not lessen these adverse effects. The increased cardiovascular risk with calcium supplements is consistent with epidemiological data relating higher circulating calcium concentrations to cardiovascular disease in normal populations. There are several possible pathophysiological mechanisms for these effects, including effects on vascular calcification, on the function of vascular cells, and on blood coagulation. Calcium-sensing receptors might mediate some of these effects. Because calcium supplements produce small reductions in fracture risk and a small increase in cardiovascular risk, there may be no net benefit from their use. Food sources of calcium appear to produce similar benefits on bone density, although their effects on fracture are unclear. Since food sources have not been associated with adverse cardiovascular effects, they may be preferable. Available evidence suggests that other osteoporosis treatments are still effective without calcium co-administration.

Reid, I. R., et al. (2011). "Calcium supplementation: balancing the cardiovascular risks." *Maturitas* **69**(4): 289-295.

Calcium supplementation has been widely accepted as a key strategy in the prevention and treatment of osteoporosis. Its role has been undermined, to some extent, by its disappointing effects on fracture in randomised controlled trials, but its use has continued to be encouraged on the grounds that it is physiologically appealing, and is [assumed] unlikely to cause harm. The latter assumption is now under threat from accumulating evidence that calcium supplement use is associated with an increased risk of myocardial infarction and, possibly, stroke. The latest data, based on meta-analysis of trials involving 29,000 participants, indicate that this risk is not mitigated by co-administration of vitamin D, and that the number of cardiovascular events caused is likely to be greater than the number of fractures prevented. These findings indicate that calcium supplementation probably does not have a role as a routine preventative agent and that dietary advice is the appropriate way to attain an adequate calcium intake in most situations. Patients at high risk of fracture need to take interventions of proven anti-fracture efficacy. Available evidence suggests that this efficacy is not dependent on the co-administration of calcium supplements.

Bolland, M. J., et al. (2011). "Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis." *Bmj* **342**: d2040.

OBJECTIVES: To investigate the effects of personal calcium supplement use on cardiovascular risk in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk. **DESIGN:** Reanalysis of WHI CaD Study limited access dataset and incorporation in meta-analysis with eight other studies. Data source WHI CaD Study, a seven year, randomised, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36 282 community dwelling postmenopausal women. Main outcome measures Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data. **RESULTS:** In the WHI CaD Study there was an interaction between personal use of calcium supplements and allocated calcium and vitamin D for cardiovascular events. In the 16 718 women (46%) who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (P=0.05 for clinical myocardial infarction or stroke, P=0.04 for clinical myocardial infarction or revascularisation), whereas in the women taking personal calcium supplements cardiovascular risk did not alter with allocation to calcium and vitamin D. In meta-analyses of three placebo controlled trials, calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% confidence interval 1.01 to 1.44), P=0.04), stroke (1.20 (1.00 to 1.43), P=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02). In meta-analyses of placebo controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from eight trials of calcium supplements and the WHI CaD participants not taking personal calcium supplements. In total 1384 individuals had an incident myocardial infarction or stroke. **Calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 to 1.45), P=0.004) and the composite of myocardial infarction or stroke (1.15 (1.03 to 1.27), P=0.009).** **Conclusions** Calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction, a finding obscured in the WHI CaD Study by the widespread use of personal calcium supplements. A reassessment of the role of calcium supplements in osteoporosis management is warranted.

Bolland, M. J., et al. (2010). "Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis." *Bmj* **341**: c3691.

OBJECTIVE: To investigate whether calcium supplements increase the risk of cardiovascular events. **DESIGN:** Patient level and trial level meta-analyses. **DATA SOURCES:** Medline, Embase, and Cochrane Central Register of Controlled Trials (1966-March 2010), reference lists of meta-analyses of calcium supplements, and two clinical trial registries. Initial searches were carried out in November 2007, with electronic database searches repeated in March 2010. **STUDY SELECTION:** Eligible studies were randomised, placebo controlled trials of calcium supplements (≥ 500 mg/day), with 100 or more participants of mean age more than 40 years and study duration more than one year. The lead authors of eligible trials supplied data. Cardiovascular outcomes were obtained from self reports, hospital admissions, and death certificates. **RESULTS:** 15 trials were eligible for inclusion, five with patient level data (8151 participants, median follow-up 3.6 years, interquartile range 2.7-4.3 years) and 11 with trial level data (11 921 participants, mean duration 4.0 years). In the five studies contributing patient level data, 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, P=0.035). Non-significant increases occurred in the incidence of stroke (1.20, 0.96 to 1.50, P=0.11), the composite end point of myocardial infarction, stroke, or sudden death (1.18, 1.00 to 1.39, P=0.057), and death (1.09, 0.96 to 1.23, P=0.18). The meta-analysis of trial level data showed similar results: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction

in those allocated to calcium (pooled relative risk 1.27, 95% confidence interval 1.01 to 1.59, P=0.038). CONCLUSIONS: Calcium supplements (without coadministered vitamin D) are associated with an increased risk of myocardial infarction. As calcium supplements are widely used these modest increases in risk of cardiovascular disease might translate into a large burden of disease in the population. A reassessment of the role of calcium supplements in the management of osteoporosis is warranted.

Gopal, A. and M. J. Budoff (2006). "Coronary calcium scanning." *Am Heart Hosp J* 4(1): 43-50.

While there is no doubt that high-risk patients (those with more than a 20% 10-year risk of a future cardiovascular event) need more aggressive preventive therapy, a majority of cardiovascular events occur in individuals at intermediate risk (10%-20% 10-year risk). Data suggest that it will be most cost-effective to concentrate screening efforts on this group of patients. Coronary artery calcium has been shown to be highly specific for atherosclerosis, occurring only in the intima of the coronary arteries. There is evidence to show that elevated coronary calcium scores are predictive of cardiovascular events, both independently of and incrementally to conventional cardiovascular risk factors. Based on current available data, patients with increased plaque burdens (increased coronary calcium scores) are approximately 10 times more likely to suffer a cardiac event over the next 3-5 years. Coronary calcium scores have outperformed conventional risk factors, high sensitivity C-reactive protein, and carotid intima-media thickness as a predictor of cardiovascular events. Both electron beam tomography and multidetector computed tomography can accurately detect and quantify the coronary calcium scores. In summary, coronary calcium detection significantly improves the accuracy of global cardiovascular risk prevention, the noninvasive tracking of the atherosclerotic burden, and the prediction of cardiovascular events.

Seelig, M. S. (1990). "Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment." *Magnes Res* 3(3): 197-215.

Prophylactic treatment of postmenopausal osteoporosis with oestrogen and calcium, often in combination, disregards the likelihood that an excess of each agent may increase magnesium requirements and decrease serum Mg levels. Relative or absolute Mg deficiency, which is likely in the Occident where the Mg intake is commonly marginal, can militate against optimal therapeutic bone response, Mg being important for normal bone structure, and can increase the risk of adverse effects. Although oestrogen has cardiovascular protective effects (expressed by the lower incidence of heart disease in premenopausal women than in men, and also in postmenopausal women given low dosage oestrogen replacement treatment), high dosage oestrogen oral contraceptives have caused increased intravascular blood clotting with resultant thromboembolic cardio- and cerebrovascular accidents. This might be contributed to by the oestrogen-mediated shift of circulating Mg to soft and hard tissues, which in persons with marginal Mg intakes may lead to suboptimal serum levels. If the commonly recommended dietary Ca/Mg ratio of 2/1 is exceeded (and it can reach as much as 4/1 in countries with low to marginal Mg intakes), relative or absolute Mg deficiency may result, and this may increase the risk of intravascular coagulation, since blood clotting is enhanced by high Ca/Mg ratios. Mechanisms by which Ca activates the various steps in blood coagulation that are also stimulated by oestrogen are considered here, as are the multifaceted roles of Mg that favourably affect blood coagulation and fibrinolysis, through its activities in lipoprotein and prostanoid metabolism.