back pain and which can be used to predict which patients will respond to placebo. A pure placebo and brain imaging study found the same results in OA patients.

Using brain coordinates from a chronic back pain study, the investigators were able to identify a prefrontal circuit that differentiates and predicts placebo responders from nonresponders with >95% accuracy. Thus, there is a brain circuit that indicates which patients will be placebo responders. "The brain predicts the future, and this may be a critical tool for future decisions about the patient," Dr. Apkarian concluded.

N-3 Fatty Acids at the Intersection of RA and CV Morbidity

Written by Rita Buckley

A meta-analysis of 17 randomized, controlled trials suggests that supplementation with oral n-3 fatty acids improves patient-assessed pain, duration of morning stiffness, and number of painful and/or tender joints in patients with rheumatoid arthritis (RA) [Bahadori B et al. *JPEN J Parenter Enteral Nutr* 2010; Kremer JM. *Am J Clin Nutr* 2007; Goldberg RJ, Katz J. *Pain* 2007]. Joel M. Kremer, MD, Albany Medical College and the Center for Rheumatology, Albany, New York, USA, reviewed studies on the efficacy of fish oil in the treatment of RA and its cardiovascular (CV) benefits.

A 24-week, prospective, double-blind, randomized trial of high and low doses of fish oil and olive oil showed significant improvements from baseline in the number of tender joints (p=0.05 for the high dose; p=0.04 with the low dose) and morning stiffness (p≤0.01) and significant decreases in leukotriene B4 and macrophage IL-1 production, especially in the high-dose n-3 fatty acid group [Kremer JM et al. *Arthritis Rheum* 1990].

A 12-month, double-blind, randomized study [Geusens P et al. *Arthritis Rheum* 1994] compared supplementation with either 2.6 mg of n-3 fatty acids or 1.3 gm of n-3 fatty acids+3 gm of olive oil. Findings indicated that 2.6 gm/day of n-3 fatty acids led to significant clinical benefit and may have reduced the need for concomitant antirheumatic medication.

According to Dr. Kremer, more than 20 peer-reviewed, blinded studies have demonstrated a consistent amelioration of tender joints in patients who have been given n-3 fatty acids versus controls of corn or olive oil. All but two studies added n-3 fatty acids to existing RA treatment regimens.

The minimal effective dose of n-3 fatty acids per day appears to be 3 to 5 g, or at least 10 capsules per day of most over-the-counter fish oil supplements. These contain about 300 mg of n-3, but "high-potency" capsules with 500 to 950 mg of n-3 are now available.

The finding that fish oil decreases CV risk is well established [Mozaffarian D. *Am J Clin Nutr* 2008; Albert CM et al. *N Engl J Med* 2002]. A protective effect seems evident at doses of long-chain n-3 fats >250 mg, much lower than those needed for symptomatic relief in RA [James M. *Proc Nutr Soc* 2010].

Fish oil may reduce CV events in RA via direct myocardial and, possibly, antithrombotic actions [Cleland LG et al. *J Rheumatol* 2006] and may also induce a favorable vascular response to ischemia [DiGiacomo RA et al. *Am J Med* 1989].

In a double-blind prospective study, 32 patients with primary or secondary Raynaud phenomenon were randomly assigned to olive oil placebo or fish oil groups. Data indicated that the ingestion of fish oil improved tolerance to cold exposure and delayed the onset of vasospasm in patients with primary (p=0.05), but not secondary, Raynaud phenomenon. The improvements were associated with significantly increased digital systolic blood pressures in cold temperatures [DiGiacomo RA et al. *Am J Med* 1989].

Dr. Kremer recommended three high-potency fish oil capsules (approximately 3 g n-3/day) in young patients with primary Raynaud, with at least 6 weeks of observation. He noted that the potential of n-3 fatty acids in the amelioration of CV comorbidity in inflammatory diseases, like RA, is worthy of further study.

Calcium, Bone Health, and CVD

Written by Rita Buckley

The benefits of calcium intake for bone health are very clear, but the risks—cardiovascular (CV), in particular—have become controversial. Richard Bockman, MD, PhD, Weill Cornell Medical College and Hospital for Special Surgery, New York, New York, USA, discussed calcium metabolism and the results of recent studies on calcium supplementation and CV health.

According to Dr. Bockman, calcium is anything but a solitary player in nutrient metabolism. "It isn't about Ca, D, P, PTH (parathyroid hormone), or FGF 23 (fibroblast growth factor 23)," he said. "It's about all of them interacting" (Figure 1). Dr. Bockman reports that when vitamin D status is sufficient, absorption of dietary calcium is approximately 30% to 40%. As vitamin D status declines, absorption of dietary calcium drops to approximately 10% to 15% (Figure 2). Low levels of calcium and vitamin D lead to increased release of PTH. This raises bone resorption and decreases bone mass.

Figure 1. Calcium Metabolism.

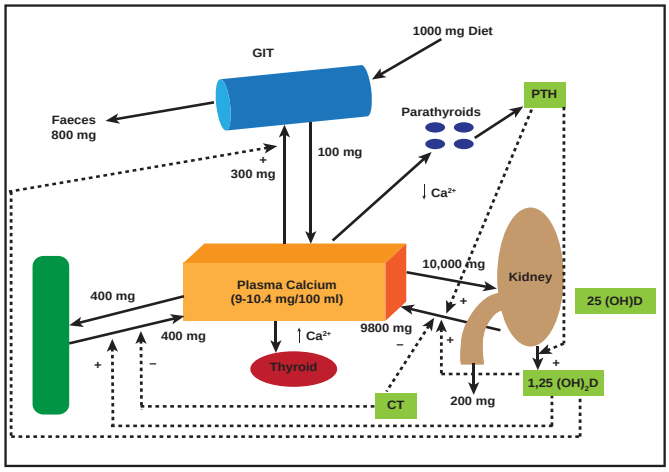

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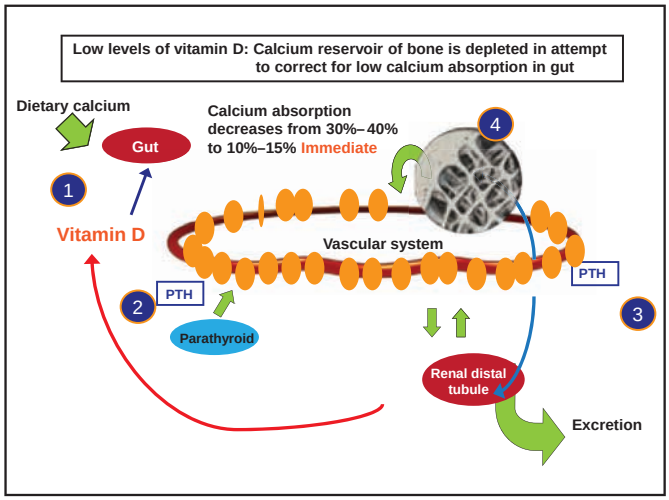
Figure 2. Interaction of Calcium, Vitamin D, and PTH with Bone and Kidney.



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Given its effect on calcium absorption, vitamin D and calcium insufficiency are associated with bone loss and increased fracture risk. Excessive P alters D, FGF, and intact PTH and increases bone loss.

Recently, the safety of calcium intake has become controversial, based on reports of increased risk of CV events that are associated with calcium supplementation (143 vs 111; HR, 1.31; 95% CI, 1.02 to 1.67; p=0.035) [Bolland MJ et al. *BMJ* 2010; Bolland MJ et al. *BMJ* 2011]. Bolland's meta-analysis from 2010 included novel datasets that were obtained from the principal investigators after the published reports, with CV outcomes obtained from self-reports, hospital admissions, and death certificates. Fifteen randomized controlled trials were eligible for inclusion—five with patient-level data and six with partially complete trial-level data.

The opposing view that calcium supplementation does not increase CV risk has also been published recently [Lewis et al. *JBMR 2010*]. A systematic review and meta-analysis by Wang et al. [*Ann Intern Med* 2010] found no increased CV risk that was associated with calcium supplementation. The authors excluded ecological, cross-sectional, and retrospective case control studies, as well as studies that did not ascertain cardiovascular disease (CVD) events (including CVD death, nonfatal coronary heart disease, myocardial infarction, and nonfatal stroke). The meta-analysis included only original study data, in which compliance was >80% and outcomes were formally collected.

According to the Institute of Medicine's review of calcium supplementation and CV risk, most studies in the meta-analyses were small and did not report dietary calcium. Vascular events were not studied as a primary outcome and were not always adjudicated. In many cases of CV events, the confidence intervals included the null association value of one. In addition, renal function was not considered a covariate in the studies, which is a well-known risk factor for CVD [Institute of Medicine: Dietary reference intakes for calcium and vitamin D. In: Washington, DC. The National Academies Press 2011].

A true placebo-controlled, randomized trial of a single, readily available nutrient, such as calcium, is often difficult to achieve. Compliance with study parameters must be maintained at levels well above 80% to provide confidence in a verifiable outcome. Clear, definable endpoints that can be validated must be used, and the most stringent methods of statistical analysis must be applied in order to provide a final answer to this complex question. Until then, the preponderance of evidence does not point to a definite conclusion regarding calcium supplementation as a cause of CV events.