Inflammation and elevation of C-reactive protein: does magnesium play a key role?

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Abstract. The adverse role played by inflammation in the etiology of human-kind’s most prevalent chronic diseases compels researchers to work diligently to explore its biologic basis. Recent research supports the concept of an important relationship between dietary factors and inflammation, and in particular the role of magnesium deficiency, however, the specifics of this association are not completely understood. Recent findings from epidemiologic studies support that magnesium intake is inversely associated with C-reactive protein concentration, an important marker of inflammation strongly associated with cardiovascular disease risk. Animal studies have provided many mechanistic possibilities to explain the link between magnesium and inflammation. Further research is needed to understand more completely the role of magnesium in inflammation.

Key words: magnesium, inflammation, C-reactive protein

As early as in 1932 there was evidence that magnesium deficiency may play a role in inflammation [1]. This observation has been confirmed by many other investigators. Bloom and colleagues demonstrated the development of a coronary arteriopathy in hamsters fed a magnesium-deficient diet for 10 days or more [2]. Affected arteries showed endothelial cell hyperplasia and pleomorphism, chronic inflammation of the media and adventitia, and fibrinoid necrosis. Lesions of myocardial ischemia, distinct from the well-known lesions of myocardial necrosis and calcification common in magnesium deficient animals, were also present. The author concluded that this vasculopathy was a new factor to be considered in the pathophysiology of magnesium deficiency. What is the evidence today for this proclamation?

Evidence of vascular inflammation also has been found in magnesium-deficient rat models, in relation to substance P [3]. More recently, Maier et al. [4] found that low magnesium concentrations impact the inflammatory response by affecting endothelial proliferation, due to an up-regulation of interleukin-1 (IL-1) and sVCAM-1, pro-inflammatory cytokines. Mazur et al. conducted a thorough review of the mainly animal evidence available at the time, and concluded that magnesium plays a significant role in the pathology of inflammation [5].

The underlying mechanisms for the inflammatory response in magnesium deficiency are not clearly elucidated. The inflammatory response includes activation of several processes which are dependent on cytosolic calcium elevation. Since magnesium frequently acts as a natural calcium antagonist, the influence of magnesium on inflammation may reflect this calcium antagonism [6, 7]. In humans, magnesium is the controlling factor for the rate-limiting enzyme in the cholesterol biosynthesis sequence that is targeted by HMG-CoA reductase inhibitor drugs (statins) [8]. As a consequence, magnesium and statins have similar anti-inflammatory effects on the HMG-CoA reductase system, including inhibiting proliferation and migration of vascular smooth muscle cells and macrophages and promoting plaque stabilization and regression. This effect offers one of several possible mechanisms for the anti-inflammatory effects of magnesium.

Another possibility is that magnesium contributes to inflammation through its effect on triglyceride levels, which increase in the face of magnesium...
deficiency [9]. This accumulation of triglyceride-rich lipoproteins is accompanied by a decrease in the concentration of high density lipoproteins and an increase in plasma apolipoprotein B concentration [5]. Because lipoprotein oxidation plays a key role in the development of atherosclerosis [10], this may be another way in which magnesium impacts the inflammatory milieu. Alternatively it is possible that the proatherogenic lipoprotein changes in magnesium deficiency are the consequence of the inflammatory response [11].

Recent epidemiologic studies provide additional evidence that magnesium may play a role in inflammation. Guerrero-Romero et al. [12] have investigated the association of serum Mg levels with CRP in obese individuals and found the likelihood of having elevated CRP, after adjustment for age, sex, BMI and glucose tolerance status, was double (Odds Ratio [OR] = 2.11; 95% CI = 1.23-3.84) for those in the lowest quintile of Mg compared to the highest. Song et al. [13] have found that Mg intake and CRP levels are inversely related among women in the Women’s Health Study (p < 0.0001), and were more strongly correlated among women with features of the metabolic syndrome. Individuals with the metabolic syndrome are characterized by magnesium depletion in addition to inflammation and high blood pressure [14, 15].

In a study by our research group of a representative sample of individuals in the US [16], adults who consumed < 50% of the RDA of magnesium were found to be more likely to have elevated CRP than adults who consumed ≥ RDA (OR = 1.75; 95% CI = 1.08-2.87). Adults over age 40 with a BMI > 25 and less than half of the magnesium RDA were even more likely to have elevated CRP (OR = 2.24; 95% CI = 1.13-4.46). These results were maintained after controlling for demographic and cardiovascular risk factors. In a second cross-sectional study, we found that magnesium supplementation lowers the likelihood of elevated CRP in people with low dietary magnesium intake by 22% [17]. This observation suggests that not only does magnesium deficiency increase inflammation, but that magnesium supplementation may be a useful strategy for reduction of inflammation, especially in people with low levels of magnesium content from foods in the diet. The study also provides important epidemiologic support for the idea that it is the magnesium itself, rather than some other component of foods high in magnesium, that is responsible for the decreased likelihood of elevated CRP.

Further evidence of a link between magnesium and inflammation in hemodialysis patients adds to the growing support for the concept of a true relationship [18]. It is likely that more connections will be found between low magnesium and inflammation as studies are conducted in specific populations with higher levels of inflammation. For example, patients with diabetes have higher levels of CRP reflecting higher levels of chronic inflammation, related to the extent of their hyperglycemia and insulin resistance [19-21]. It is therefore no surprise that recent studies have found evidence of low magnesium in such populations [22, 23].

More recent epidemiologic studies in children support a role for magnesium in inflammation and a lifelong physiologic mechanistic process. Researchers conducted an analysis in the cross-sectional, nationally representative National Health and Nutrition Examination Survey (NHANES) focused on children aged 6-17 years [24]. Children consuming less than 75% of RDA were twice as likely (p < 0.05) to have elevated serum CRP levels as children consuming above the RDA. In adjusted analyses controlling for demographics, cardiovascular risk factors, and BMI, children with a consumption of less than 75% RDA remained more likely to have elevated CRP (OR = 1.58; 95% CI = 1.07-infinty).

In inflammation, what role is played by magnesium deficiency? From emerging evidence, it is apparent that magnesium, while perhaps neither necessary nor sufficient for inflammation on its own, plays a key role in potentiating inflammatory processes that contribute to atherosclerosis. Rayssiguier’s recent paper illuminates this concept, by observing that inflammation may be more pronounced in the context of higher fructose consumption and low dietary magnesium intake [25]. Guerrero-Romero and Rodriguez-Moran [15] have similarly tied together hypomagnesemia with inflammation and oxidative stress. It is precisely this type of observation that needs to be further explored. Learning more about how magnesium works in combination with other key dietary factors may illuminate its role as an important modulator of inflammation and further unlock the secrets of clinical inflammation.

References


