**Biomarker of Magnesium Status in Response to Mg Supplementation: A Dose- and Time-Response Meta-analysis of Randomized Controlled Trials**

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Short title: Magnesium Biomarkers in RCTs

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**ABSTRACT**

**Background:** Magnesium is a cofactor for hundreds of human enzymes and magnesium deficiency has been associated with cardiometabolic disorders. Although a panel of magnesium biomarkers are used to assess magnesium status, their relative predictive values or clinical usefulness in response to magnesium supplementation remain unclear.

**Objective**: We quantitatively evaluated time- and dose-response relation of magnesium biomarkers from available randomized controlled trials (RCTs) of magnesium supplementation.

**Methods:** We systematically identified RCTs assessing magnesium biomarkers' responses after oral magnesium supplementation through search on MEDLINE and Cochrane Library up to November 2014. We calculated the pooled weight mean differences (WMDs) of biomarkers levels between treatment and placebo group after supplementation. A dose- and time-response meta-analysis was conducted to quantitatively compare the usefulness of biomarkers in assessing magnesium status.

**Results:** This meta-analysis included 44 RCTs of magnesium supplementation that examined a total of 38 biomarkers of magnesium status. Total magnesium concentrations in blood (serum or plasma), RBC, and urine were significantly raised after magnesium supplementation by 0.05 mmol/l, 0.12 mmol/l, and 1.52 mmol/24h corresponding to 5.81%, 5.30%, and 28.3% increases relative to baseline magnesium levels, respectively. Our dose- and time-response meta-analyses showed that blood and urinary magnesium levels abruptly increased at the first 20-week supplementation and afterwards reached a plateau. Evidence was insufficient due to limited numbers of studies testing other potential biomarkers, including ionized Mg, muscle Mg, mononuclear Mg, intracellular Mg, IV Mg load, ultrafiltrable Mg, and fecal Mg.

**Conclusions:** This meta-analysis of available RCTs demonstrated that blood total magnesium and 24-h urinary magnesium levels are reliable biomarkers with stable change patterns in response to magnesium supplementation in a dose- and time-response manners. Further large well-designed RCTs are needed to determine clinical usefulness of other potential biomarkers.

**Keywords:** magnesium status, magnesium biomarkers, meta-analysis, randomized controlled trial, sensitivity, usefulness.