

Serum magnesium: a biomarker of cardiovascular risk revisited?

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Magnesium (Mg) is integral for modulation of vascular tone and cardiac electrophysiology. The sodium potassium pump, which regulates ion currents across the cell membrane, is among the over 300 enzyme systems Mg activates [1]. Mg blocks slow inward calcium currents and prolongs atrioventricular conduction [2]; myocardial Mg insufficiency decreases intracellular potassium, which increases susceptibility to arrhythmias [3-5]. Two randomized, controlled, double-blind, dietary Mg depletion studies that reduced the Mg intake of postmenopausal women to 33-50% of the recommended dietary allowance (RDA) for Mg, in diets not considered atypical Western menus, reported supraventricular ectopy, flutter and atrial fibrillation in some participants [6, 7]. Since calcium, potassium, copper and other nutrients were supplemented during the Mg depletion phase [6], and arrhythmias were relieved by Mg supplementation, this work suggests that inadequate Mg intake can be arrhythmogenic. The following commentary reviews serum Mg (sMg) as a biomarker of Mg status and intake, and argues that sMg may best be characterised at present, as a biomarker of cardiovascular risk.

Assessment of Mg status using an accurate, rapid, non-invasive test remains a challenge to modern medicine. Access to the two largest compartments of total body Mg, bone and muscle, requires invasive procedures [8, 9]. While the Mg loading test, which measures urinary Mg excretion, is the gold standard for the assessment of

Mg deficiency, it is resource-intensive and inappropriate for patients with kidney and intestinal disorders, particularly when Mg is orally administered [10]. In adults, only 25% of total body Mg can be studied using stable isotopes, which capture rapid exchanges between body Mg pools [11]. Assessment of free (ionized) Mg using ion selective electrodes may be subject to inaccuracies from pH effects and/or interferences from ionized calcium, and thiocyanate in smokers [12].

sMg is the most widely measured Mg biomarker clinically and in epidemiological studies, since abnormally reduced sMg concentrations strongly suggest underlying Mg deficiency [13]. Although inexpensive and accessible, there are important limitations of sMg as a biomarker of Mg status. sMg is maintained within 0.75-0.955 mmol/L in healthy adults by dietary absorption of Mg from the gastrointestinal track and renal excretion [10, 14]. Approximately one third of skeletal Mg is exchangeable and may serve as a reservoir for maintaining sMg within the reference interval [15, 16]. Thus, although sMg may be within the reference range, chronic latent Mg deficiency may be present, in which there is a depletion of total body Mg as determined by the Mg loading test [15, 16].

As sMg has not been validated as a reliable indicator of total body Mg status [13], its predominant use as an Mg measure over the decades might be justified by evidence that this biomarker is a surrogate for Mg dietary intake, implying that sMg might be highly modifiable. In fact, there

is little evidence that sMg is closely associated with dietary Mg, neither is there convincing evidence that sMg is highly modifiable in individuals with normal baseline Mg concentrations. The correlation coefficient (r) between sMg and dietary Mg ($n = 14,882$) was <0.06 in all race and sex groups in the Atherosclerosis Risk in Communities cohort [17] and <0.12 in other populations [18, 19]. Consistent with observations that sMg is under tight homeostatic regulation [20] and may be compensated by bone pool Mg [10], it has been demonstrated that while sMg initially decreased during controlled, dietary Mg deprivation, it rebounded to baseline values on day 40 and only slightly decreased thereafter [6].

Further, Mg biomarkers and dietary Mg may be associated with different risks of cardiovascular events. In the ARIC cohort, a significantly reduced risk of sudden cardiac death in the highest compared to the lowest quartile of sMg was reported (RR: 0.62; 95% CI: 0.42-0.93), but dietary Mg was not associated with risk of sudden cardiac death [21]. Similarly, a weaker association between dietary Mg and sudden cardiac death was observed in the Nurses' Health Study [18]. In women of the ARIC cohort, sMg, but not dietary Mg, was significantly inversely associated with coronary disease [22].

While lack of associations between dietary intakes of nutrients and nutrient biomarkers are sometimes attributed to imprecision in dietary measuring tools, recent Mg interventions [23-25] and a systematic review [26] report only modest changes in sMg in adults with normal sMg concentrations at baseline. Among obese, nondiabetic adults, sMg concentrations increased only slightly (0.90 ± 0.08 mmol/L to 0.92 ± 0.07 mmol/L) after six months of Mg supplementation (365 mg/day) [25]. In a meta-analysis of Mg supplementation in type 2 diabetes (median: 360 mg/day for three months), the weighted mean difference in Mg biomarkers was 0.06 mmol/L higher in the treatment group, with no linear trend and a complex relationship to the time course of supplementation [27]. In an experimental Mg dietary deprivation study, mean sMg concentrations declined from 0.860 ± 0.007 mmol/L to 0.830 ± 0.007 mmol/L when postmenopausal women consumed a 130 mg/day Mg diet for 81 days *versus* a 411 mg/day Mg diet for 81 days [7]. These sMg changes are small relative to the range of the reference interval for sMg (~ 0.75 - 0.955 mmol/L) [14], and while it is clear that

improved understanding of sources of heterogeneity in the responsiveness of sMg to intervention is required, if sMg associations with cardiovascular risk are causal, larger changes might be needed in order to maximize cardiovascular risk reduction [18, 21, 22].

A final observation suggesting the inadequacy of sMg as a dietary Mg biomarker is that nondietary factors significantly influence sMg concentrations. While diabetes, even for transient periods, is associated with altered Mg homeostasis and concentrations [13, 19], kidney and gastrointestinal diseases [28], moderate alcohol consumption [29], and use of some cardiovascular drugs (e.g. diuretics) increase Mg loss and are associated with sMg depletion [30].

To summarise, if there is no convincing evidence that sMg is a good biomarker of Mg status, nor a good biomarker of dietary Mg, and is subject to multiple, often incompletely measured external influences, what purpose does it serve? sMg warrants further investigation as a cardiovascular risk biomarker. One important finding from most, but not all recent investigations [31], is evidence of cardiovascular risk stratification across the sMg concentration range (*table 1*). Significantly decreased fasting glucose and carotid intima-media thickness across the sMg concentration gradient among nondiabetic adults have been observed [17, 32]. A graded, reduced prevalence of premature ventricular beats across the sMg concentration range has been reported in the Framingham Offspring cohort and in a population sample of adults with type 2 diabetes [33, 34]. In the Study of Health in Pomerania (SHIP), low sMg concentrations were associated with increased left ventricular mass independent of common cardiovascular risk factors [35], cardiovascular mortality and higher all-cause mortality [36]. Similarly, an inverse association between sMg and mortality from ischaemic heart disease and all-cause mortality was observed in the National Health and Nutrition Examination Survey (NHANES) cohort [37]. Consistent with evidence of cardiovascular risk stratification within the sMg reference interval, it has been argued that the traditional method to establish a reference interval for sMg is flawed, since there may be a large number of 'normal' range individuals with subtle chronic negative Mg balance [38].

In conclusion, sMg may have some use as a biomarker for cardiovascular risk. If coronary risk is stratified across the concentration range

Table 1. Serum magnesium (sMg) and cardiovascular endpoints in large, prospective cohorts

| Study | Cohort | n | Outcomes | Follow-up (yrs) | Findings |
|---------------------------------------|--|--------------------------------|----------------------------------|-----------------|---|
| Liao <i>et al.</i> , 1998 [22] | ARIC | 13,922 | Coronary heart disease | 4-7 | Q4 <i>versus</i> Q1 sMg: RR 0.44 (0.22-0.92) in women; 0.73 (0.47-1.13) in men* |
| Ford <i>et al.</i> , 1999 [37] | NHANES | 12,340 | Ischemic heart disease mortality | 19 | Q4 <i>versus</i> Q1 sMg: HR 0.69 (0.52-0.90)† |
| Peacock <i>et al.</i> , 2010 [21] | ARIC | 14,232 | Sudden cardiac death | 12 | Q4 <i>versus</i> Q1 sMg: HR 0.62 (0.42-0.93) ‡ |
| Khan <i>et al.</i> , 2010 [31] | Framingham Offspring | 3,531 | Cardio-vascular mortality | 20 | Per 0.06 mmol/L sMg increment: HR 0.83 (0.49-1.40) § |
| Reffleemann <i>et al.</i> , 2011 [36] | SHIP | 3,910 | Cardio-vascular mortality | 10.1 | sMg ≤ 0.73 <i>versus</i> > 0.73 mmol/L: HR 1.66 (1.13-2.45) |
| Chiuvè <i>et al.</i> , 2011 [18] | Nurses' Health Study (nested case-control study) | 99 cases, 291 matched controls | Sudden cardiac death | (up to) 16 | Q4 <i>versus</i> Q1 (plasma) Mg: RR 0.23 (0.09-0.60) ¶ |

Q: Quartile

* Relative risk (RR) adjusted for age, race, ARIC field center, waist/hip ratio, smoking, alcohol, education, sports index, fibrinogen, total & HDL cholesterol, TG, diuretic use & hormone replacement therapy (women)

† Hazard ratio (HR) adjusted for age, sex, race, BMI, physical activity, alcohol, education, smoking, cholesterol, systolic blood pressure, antihypertensive medication use, diabetes

‡ HR adjusted for age, race, sex, ARIC field center, HDL, LDL, TG, serum potassium, heart-rate adjusted QT interval, physical activity, current smoking, pack-years, alcohol, education, diabetes, hypertension, diuretic use

§ HR adjusted for age, sex, diabetes, systolic blood pressure, total/HDL ratio, smoking, hypertension treatment, haemoglobin, serum albumin, glomerular filtration rate

|| HR adjusted for age, sex, diabetes, BMI, glomerular filtration rate, arterial hypertension, use of calcium agonists, beta blockers, diuretics, statins, ACE and angiotensin receptor inhibitors

¶ RR adjusted for age, fasting, parental history of myocardial infarction, alcohol, physical activity, postmenopausal hormone use, diuretics, aspirin use, intake of magnesium, long-chain omega 3s, calcium, potassium, and vitamin D, C-reactive protein, glomerular filtration rate, HDL cholesterol, N-terminal pro-B type natriuretic peptide, history of diabetes and hypertension

of a key electrolyte, failure to invest research efforts in such cardiovascular fundamentals, in our sophisticated medical age, would be a potential opportunity lost.

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