Re-evaluation of the concept of chronic, latent, magnesium deficiency

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I appreciate the opportunity to comment on Dr Günther’s letter on “Magnesium in bone and the magnesium load test” [1]. He appropriately raises the question of whether the concept of chronic latent magnesium deficiency (CLMD) should be re-evaluated. I coined the term CLMD several years ago to describe individuals who have a small, chronic, negative magnesium (Mg) balance, but whose serum Mg concentration is within the lower part of the reference interval (latent), and from a clinical standpoint are viewed as having normal Mg status [2]. I recently updated the concept of CLMD in this journal [3]. The reference interval for serum Mg concentrations was determined to be 0.75 to 0.955 mmol/L, with a mean concentration of 0.85 mmol/L in a US population of 15,820 individuals between the ages of 18 and 74 years, which were part of the NHANES I Study [4]. I have defined CLMD as a serum Mg concentration of between 0.75 and 0.849 mmol/L (within the reference interval), with a positive Mg load test (MLT) indicating Mg deficiency. I refer to figure 1 in that recent publication, which identifies the three factors leading to a chronic, negative Mg balance; inadequate intake, decreased gastrointestinal absorption, and increased excretion by the kidneys. The most common cause of CLMD is probably inadequate intake based upon the progressive decrease in the Mg content of our diet over the past century due to processing of food and fast foods [5, 6]. Other significant entities causing a chronic, negative Mg balance are diseases such as diabetes mellitus, alcoholism and a growing list of drugs that compromise reabsorption of Mg by the kidney. The status of a small, chronic, negative Mg balance may go on for years, or indeed a lifetime.

As pointed out by Dr Günther, about 50-70% of body Mg is localized in bone and about 30-50% is exchangeable [1]. Studies by Alfrey et al. found an excellent positive correlation (r=0.96) between bone Mg concentration and the serum Mg concentration [7]. This study supports the concept that the exchangeable bone Mg may serve as a reservoir of Mg that acts to maintain a normal serum Mg concentration. However, the equilibrium among most tissue compartments for Mg is reached very slowly, if at all. Studies suggest that the biological half-life of the majority of Mg in the body is between 41 and 181 days [8, 9]. The serum Mg concentration is more labile than the bone Mg content since Mg absorption from the gastrointestinal tract and excretion by the kidneys are continuous processes that act to adjust the serum Mg concentration. For an individual that has a Mg deficiency, the exchangeable bone Mg fraction probably supplements the serum Mg concentration slowly, to achieve a serum Mg concentration within the lower part of the reference interval. It is upon this basis that I have proposed an evidence-based value for the lower limit of the reference interval for health and normal Mg status, of 0.85 mmol/L [3]. Thus, it seems plausible that if an individual has a small, chronic, negative Mg balance for an extended period of time, there is a reduction in the bone Mg content, and the serum Mg concentration will be in the lower part of the reference interval or even below the lower limit.

The MLT was proposed as a more sensitive test to determine Mg deficiency (total body Mg deficit) than the serum Mg concentration [10]. After all, it is relatively common to have a serum Mg concentration within the reference interval,
but yet a total-body Mg deficit. The MLT is a physiological test with many variables and is unique for an individual. The premise for the MLT assumes that bones deficient in Mg would take up intravenously-administered Mg, and thus the excretion of Mg would be reduced over a short time interval, usually 24 hours, which is measured as percentage retention [10]. A further assumption is that the individual has relatively normal renal function. One study has concluded that the MLT “is of limited routine clinical value in older subjects” [11]. Of importance is that two independent studies have found a very significant negative correlation (r = -0.99 and -0.71, p < 0.001 respectively, for the two studies) between the MLT and bone Mg concentration [12, 13]. Thus, studies have shown a significant correlation for bone Mg concentration with both the serum Mg concentration (positive) and the MLT (negative).

Dr Günther cites the paper by Cohen et al. [14], and states “it cannot be explained why normomagnesemic osteoporotic patients retained more Mg than controls and why normomagnesemic diabetics, with the same reduction in bone Mg content and the same alteration in bone mineral crystallinity, did not show an abnormal Mg retention” [1]. In this study, the osteoporotic patients have a mean serum Mg concentration of 0.80 mmol/L (compared with the control of 0.875 mmol/L), and an abnormal MLT mean of 38% retention. These osteoporotic patients exhibit CLMD, with a serum Mg concentration within the reference interval (but below my proposed cut-off of 0.85 mmol/L for health) and an abnormal MLT indicating Mg deficiency. On the other hand, the diabetic patients in this study, who have a mean serum Mg concentration of 0.86 mmol/L (greater than my cut-off of 0.85 mmol/L), and a normal MLT with 12% retention, do not have CLMD. I cannot explain the results for women taking an oral contraceptive preparation, but would speculate that it may be related to a drug effect. I agree with Dr Günther that “the localization and state of the nonexchangeable bone Mg are not defined” [1]. The exchangeable Mg in bone probably resides in the hydrated layer adjacent to the apatite core [15]. Dr Günther postulates that in the MLT, the Mg uptake by bone “depends on the total surface of the apatite crystals” [1]. However, it may be that it is the hydrated layer, next to the apatite core, that has the greater responsibility for the results of the MLT. Further, Dr Günther cites a study where the “reductions in bone Mg content exceed the normal exchangeable bone Mg content, indicating an alteration in bone mineral state” [1]. He asks the question as to whether these changes are “caused by Mg deficiency or by changed activity of bone cells?” I think this is a valid question, but it highlights the complexity of the status of bone Mg and how it might be altered in healthy and diseased individuals. Certainly, this area is deserving of further research to understand better bone Mg metabolism. Thus, in my opinion, the examples of the osteoporotic and diabetic patients cited by Dr Günther are consistent with the concept of CLMD. Is there a need to re-evaluate CLMD or do we need a better understanding of bone Mg metabolism?

References


