Magnesium intervention studies - methodological aspects

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There is an abundance of data regarding the importance of magnesium (Mg) in a variety of human functions such as regulation of muscular tonus, insulin sensitivity, and cardio-vascular function [1-4]. In spite of this the results from intervention studies with the aim to ameliorate or prevent pathological processes in relation to these mechanisms remain less convincing. A meta-analysis of the effect of Mg on blood pressure concluded that there was no robust evidence that oral Mg supplementation reduces high blood pressure in adults [4]. It is likely that several of the intervention studies are influenced by methodological problems. The aim of this review is to focus on some important such problems and suggest how they can be avoided in studies on intervention with Mg.

Mg homeostasis

Mg homeostasis is regulated by its uptake through food and drinking water, the degree of renal reabsorption of Mg, and its loss through sweating. Renal reabsorption is decreased in the elderly and under acid urine conditions, such as after eating large amounts of protein [5]. Many studies have shown that the Mg intake from food is related to economic status, population characteristics, and age. A skewed distribution of these characteristics within population samples undergoing placebo/intervention studies will thus represent an important methodological error.

Clinical methods to identify a low Mg status are not very precise as plasma and blood levels show little variation and values within the usual reference range do not exclude deficiency [6, 7]. A selection of people using only the criterion “low plasma levels” will comprise only those with a severe Mg deficiency. It will not include those with suboptimal Mg status that would also benefit from Mg supplementation. An alternative to defining Mg status is to use nutritional questionnaires, selecting those with a low consumption of food items rich in Mg.

An omission of a measure of Mg status means that subjects that are not in need of Mg and who will thus not respond to Mg supplementation will be included in the study. The number of people requiring Mg is thus diluted and differences between Mg and placebo groups might not reach statistical significance.

The importance of drinking water as a source of Mg has often been neglected. One study compared people living in areas with different Mg levels in the drinking water. They found a significantly higher level of Mg in muscle tissue among those living in areas with high levels of Mg in the drinking water [8]. Several studies have reported an increase in cardiac infarction among people living in areas with low levels of Mg in the drinking water [9-13]. Intervention studies with populations from areas with different levels of Mg in the drinking water would thus pose a potential methodological problem in terms of the stratification with regard to risk groups.

Several of the diseases where Mg supplementation has been investigated have a multifactorial origin and the possibility of detecting an effect thus depends on the proportion of subjects with a low Mg status in the study cohort. An example is a study which evaluated the relationship between mortality in cardiovascular disease and the level
of Mg in drinking water [11]. When the whole group was evaluated, no relationship was found, but when subgroups were analysed, males with a low consumption of Mg-rich vegetables were found to have a significantly higher risk. They thus comprised a risk group.

**Individuals at risk**

A major cause of Mg deficiency is differences in the Mg content of food or water consumed. Impaired renal reabsorption of Mg as a result of age or acid conditions is also important. The relation between the acid-base balance and urinary excretion of Mg was investigated in a population sample of people above 50 years of age and with no disease [14]. The urinary excretion of urea (a proxy for acid load), and magnesium were measured in 24-hour urine samples. Even though there was a significant relationship between urea and Mg excretion (correlation coefficient = 0.373, p = 0.025), a number of subjects with high levels of urea had rather low urinary values of Mg. Hence, this population was divided into those with a urea excretion below or above the second quartile (393 mmol/24 h). In the group with high urea excretion, there was an inverse relationship between systolic blood pressure and the excretion of Mg (correlation coefficient = -0.747, p = 0.008). These data suggest that people who have low urinary excretion of Mg, in spite of high acidity, might have a deficiency in Mg, which manifests itself as increased blood pressure. Intervention experiments with a focus on this risk group would yield further information on the importance of Mg deficiency in increased blood pressure.

In one study, subjects received bottled water, with or without Mg. Subjects consuming the Mg-rich water experienced a decrease in blood pressure, but this was confined to those with a low excretion of Mg in the urine [15]. These data are supported by a study where a reduction in blood pressure after Mg treatment was found only in the group with a low, initial, urinary secretion of Mg [16].

**Effect evaluation**

The traditional method for evaluating the effect of Mg on blood pressure is to calculate means in the group studied at different time intervals after the initiation of the study. This procedure does not take into account the concept of risk individuals and their importance in the group. A relationship between blood pressure and Mg could only be present among risk individuals. This concept is illustrated in the previously cited meta-analysis [4]. The largest effect of Mg on blood pressure was found in a study where the initial high blood pressure was higher than in other studies. When this study was excluded from the meta-analysis, the effect of Mg on blood pressure was considerably smaller. Other review studies have not commented upon the importance of risk groups [2, 4, 17].

The insensitivity of using average blood pressure for the whole group is illustrated in a study where Mg supplementation was given to pregnant women throughout the pregnancy [18]. When the average systolic and diastolic blood pressures were evaluate at different time intervals, there were only minor difference between the intervention group and the placebo group. When the results were evaluated as the number of people showing an increase of ≥15 mmHg, the difference was significant at week 37, and borderline significant at weeks 35 and 39. Those with an increase in diastolic blood pressure of ≥15 mmHg had higher urinary Mg excretion at week 12.

**Therapeutic range**

The therapeutic range of Mg, i.e. the difference in intake between controls and those subject to intervention is an important issue. One study found no effect of Mg supplementation on blood pressure during pregnancy [19]. The dose was 2×67 mg Mg. This is a low dose in comparison to the recommended intake, which is around 250-350 mg Mg, and in comparison to other supplementation studies that usually recommend 300-400 mg Mg. One study on pregnancy hypertension used 370 mg Mg, but the control group also received Mg at 100 mg [20]. The therapeutic dose was 270 mg, which might be the reason why no effect was found. Another possible reason for the absence of an effect is that a basic supplementation with 100 mg might have been sufficient to restore a deficiency in some cases, thus reducing the number of subjects where an effect could be expected.
Compliance

Compliance with supplementation is a methodological problem. Some subjects forget to take the supplementation or abstain for longer periods because of perceived complications when taking the supplement. Other subjects may know of the beneficial effect of Mg and obtain the preparation themselves. There are no precise methods to control for a proper supply of Mg. The only way to control for this potential error is repeated questions on compliance throughout the study, with details recorded in the description of methods. Suspect subjects should then be excluded.

Type of Mg preparation

The type of Mg preparation used for supplementation may influence the efficiency of the supplementation. An extensive review of bioavailability and pharmacokinetics concluded that Mg salts of organic acids have greater water solubility and therefore greater bioavailability than inorganic sources of Mg [21]. A review of the relatively few studies performed on absorption concluded that organic salts of Mg such as citrate have the best absorption rates [22].

Comments

Data from many studies strongly suggest that the general population comprises a mixture of subjects with large differences in Mg homeostasis. Such differences need to be recognized and corrected for in the selection and analysis of subjects in intervention studies. Otherwise there is a risk that negative results in intervention studies might not be due to an absence of an effect, but to heterogeneity regarding Mg homeostasis in the population studied.

Disclosure


References


