Magnesium and healthy aging

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Abstract. Magnesium (Mg) is relatively stable in the intracellular compartment, although decreases linearly with advancing age. This begs the question as to whether Mg could be used as biomarker of aging. A biomarker of aging is a biological parameter of an organism that, in the absence of disease, better predicts functional capability at a later age than the chronological age. Bone and muscle Mg content might be useful biomarkers, but the need for biopsies and the heterogeneous distribution of Mg in bones and muscles strongly limit the application of these methods in clinical practice. Similar considerations can be made for urinary Mg assessment, particularly after a loading test. Markers of Mg in blood seem fairly unreliable as biomarkers of aging since they are strongly dependent upon renal function, do not reflect the intracellular Mg status, and, in some investigations, are within normal ranges although other Mg parameters are not. Other investigations (e.g. nuclear magnetic resonance with fluorescent probes) seem to be promising, but their availability remains limited.

Key words: magnesium, marker, healthy, aging

Mg is an important regulator of energetic metabolism, muscle contraction and neurological functions. Indeed, Mg is involved in many intracellular pathways, being a co-factor for over 300 enzymes [1-3].

Although the total amount of Mg tends to decrease with advancing age [4], it is not completely clear if the pathological conditions associated with aging or aging per se are the cause of this physiological reduction. Mg deficiency, in fact, is common in several conditions typical of older people [5-10], and this opens the debate whether Mg could be used as marker of healthy aging and which parameter might be the best to estimate Mg status in the elderly.

In this work, we would like to offer a point of view about the physiological role of Mg in the elderly, and discuss whether Mg could be used as marker of healthy aging.

Aging and magnesium deficiency

About 55-65% of the body's magnesium is stored in bone. Therefore, the reduction in bone mass in older people is often associated with a reduction in total body Mg [4]. Although the Mg stored in bone is not easily exchanged, a reduction in stored Mg might contribute to poor Mg status overall, and possibly to hypomagnesemia [4]. However, some researches have proposed that low serum levels of Mg might be a risk factor for osteoporosis, especially in postmenopausal women [11]. Therefore, bone mass and serum Mg could influence each other.

The changes in the metabolism of Mg in the elderly can be classified as primary or secondary [4]. Primary causes are physiological changes of aging, such as inadequate dietary Mg intake, reduced absorption from the gastrointestinal system and increased urinary excretion of Mg because of decline in renal function. Conversely, causes of secondary Mg deficiency are conditions related to age, particularly insulin resistance, type 2 diabetes mellitus and metabolic syndrome, and increased urinary Mg loss secondary to drugs (loop diuretics, digitalis, and possibly proton-pump inhibitors).

Sub-clinical Mg deficiency, ensuing from these changes, might also have a role in promoting low-
grade inflammation, a condition that seems to be a feature in several medical conditions [4, 8, 12]. This has been confirmed by recent work showing an inverse association between dietary Mg intake and serum C-reactive protein level [13]. In animal models [14], a low dietary intake of magnesium leads to an increase in serum levels of IL-1, IL-6, TNF-α and substance P, which induce liver production of acute phase proteins and neutrophils/macrophage more responsive to activation by immune stimuli with oxidative stress. It is possible that the inflammation increases because Mg is a calcium antagonist: a low dietary intake of Mg, in fact, leads to decline in extracellular Mg and a consequent increase in the influx of calcium into cells [13-15]. This evidence supports a pleiotropic action of Mg, particularly in older people in which several conditions (primary or secondary) could jeopardize a good Mg status.

Magnesium as biomarker of healthy aging

Sprott closely analyzed the problem of the “ideal” biomarker of aging. Briefly, the concept of biomarkers of aging and age-related disease dates to the early 1980s as scientists engaged in aging research worked to better define aging and the most common medical conditions typically associated with it [16].

A biomarker of aging is a biological parameter of an organism that, in the absence of disease, better predicts functional capability at an age later than chronological age [17]. Ideally, a biomarker of aging should be easily measurable, lower in pathological conditions than in a healthy status, should decrease with advancing age, and be poorly influenced by a decline in regulatory systems, such as renal function. In addition to intracellular and nuclear markers (e.g. telomere length) [18], several biomarkers of aging found in blood have been proposed, namely serum 25-hydroxyvitamin D [19], dehydroepiandrosterone sulphate [20] and oxidative stress/inflammation markers [21].

In this context, Mg could also be considered to be a potential biomarker of aging, although there are some considerations, the most important being, what is the best indicator of Mg status in older persons? Since bone and muscle are the major deposits of Mg in the body, ideally, intracellular measurements in these compartments are the best indicators of Mg status. However, the necessity for biopsies and the heterogeneous distribution of Mg in bones and muscles strongly limit the application of these methods in clinical practice [22, 23]. Similar considerations can be made for urinary Mg assessment after a loading test, as this is very time-consuming, requires trained staff, and no standardized protocols are available [23].

In table 1 we summarized the most common methods for assessing Mg in clinical practice, discussing also whether they can be used as biomarkers of aging. Serum Mg is the most common method for estimating Mg deposits, but it is probably not that reliable as a biomarker of healthy aging, being often normal, despite the presence changes in other indicators of Mg. In a study involving 36 healthy, older subjects, Gullesstad et al. [24] reported normal values for serum Mg, but about a quarter of the participants were found to be in a state of sub-clinical Mg deficiency when investigated using a 24-h Mg retention after a Mg load procedure. We recently confirmed these findings, reporting a prevalence of about 5% for sub-clinical Mg deficiency, as determined by 24-h urine collection in older women with normal serum Mg values [25]. Therefore, these findings suggest that other methods of assessment of Mg status could be more reliable for determining the existence of Mg deficiency in older people. There has been an extensive study involving red and white blood cells, and although the methods used had the advantage of offering intracellular estimation, which could be important since Mg is mostly an intracellular mineral, the results seem to correlate poorly with body tissue Mg. In addition, studies in the elderly were very few [23].

Twenty-four urine Mg collection is considered a better marker of Mg status than serum Mg by several authors [26, 27], however, there is not universal consensus on this subject. Timed 24-h urine collections can be used to determine accurately magnesium absorption and deposits [28], and prospective studies have shown that low 24-h urinary Mg excretion is prospectively associated with an increased risk of cardiovascular diseases [26, 27]. However, this method has several limitations for older people, including difficulty in collecting urine (particularly in women), bias in reporting the correct quantity of urine collected, and the huge interference due to drugs such as diuretics.
Table 1. Magnesium parameters used as biomarkers of aging.

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Inexpensive</td>
<td>No correlation with tissue pools of magnesium</td>
<td>In healthy, older subjects, it seems that serum Mg is normal, but sub-clinical Mg deficiency could be common</td>
</tr>
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<td></td>
<td>Available in all laboratories</td>
<td>Only 0.3% of total Mg in the body is in the serum</td>
<td></td>
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<td></td>
<td>Indicator of acute changes in Mg status</td>
<td>Not all studies reported changes in serum Mg following changes in dietary Mg intake</td>
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<tr>
<td>Red blood cells</td>
<td>Reflects intracellular storage of Mg better than serum/plasma Mg</td>
<td>No clear correlation with Mg in body tissues</td>
<td>Although red blood cells reflect an intracellular Mg deposit, there is no universal consensus concerning its use in healthy, older people</td>
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<td></td>
<td>Decreases linearly with aging, although serum Mg is within normal range</td>
<td>Genetic regulation seems to be relevant</td>
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<tr>
<td>Plasma</td>
<td>Inexpensive</td>
<td>Anticoagulant used for blood tests could lead to unreliable results</td>
<td>Between serum and plasma Mg, serum is preferred since it does not depend on the measurement methods</td>
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<tr>
<td></td>
<td></td>
<td>Does not reflect the amount of Mg stored in body tissues</td>
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<tr>
<td>Free</td>
<td>Does not depend on protein quantity, unlike serum Mg</td>
<td>Thiocyanate: increased in blood of smokers, has a negative interference with this parameter</td>
<td>Only a few laboratories can measure this parameter that seems not to offer significant advantages compared to serum Mg</td>
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<tr>
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<td>Biological functions in blood</td>
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<tr>
<td>24h-urinary</td>
<td>Linearly reflects Mg introduced with diet Correlates with Mg stored in body tissues</td>
<td>Difficulty of collection, particularly in older women Possible biases in reporting correct amounts of urine</td>
<td>Probably, this is the best estimator of Mg status in the elderly, even if it seems reliable only in healthy subjects, due to difficulties in collection</td>
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</table>

Abbreviations: Mg: magnesium

Thus, other and more sophisticated methods are probably needed in order to allow Mg to be used as a biomarker of healthy aging. Ideally, these markers should reflect the total amount of Mg in the body and not depend on changes in dietary Mg intake. In this context, nuclear magnetic resonance with fluorescent probes could represent a tool for a better estimation of Mg status, which could then be used as biomarker of aging.

Conclusion

Mg might represent a good marker of healthy aging since it decreases linearly with aging, and it is usually lower in pathological conditions (such as inflammation) compared to a healthy status in older subjects. Although intriguing, further research involving the optimal method for assessing Mg in older subjects is needed to confirm whether Mg could be used as biomarker of aging.

Disclosure


References


