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Magnesium and Hip Fractures: An Overlooked Macro Mineral?

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Abstract

Introduction: Hip fractures, which remain highly prevalent oftentimes life-threatening events among older populations, are highly challenging to prevent and treat effectively despite years of multiple related endeavors.

Objectives: This mini-review strove to examine whether: 1) magnesium, an important dietary compound is a relatively unrecognized, and hence underutilized potentially important hip fracture determinant among the older at risk adult, and 2) whether more research and consideration of its nutrient properties in this realm is warranted.

Methods: Relevant data concerning this topic sought from three well-established preselected electronic data bases housing English language research or commentary reports published over the last 40 years (1980 - 2020) were carefully examined. Reviewed specifically were representative recent studies and reviews, including their conclusions regarding the possible relevance of efforts to assess and treat magnesium deficits in the context of hip fracture prevention among the elderly.

Results: Despite quite compelling basic research showing a high number of magnesium-dependent health interactions that impact well-being across the lifespan, including bone health, very few explicit or targeted studies on the present topic were located. However, among those located, most if not all, point to a potentially important clinically relevant association between magnesium and hip fractures.

Conclusion: More intense and thoughtfully designed research to examine the multiple ways magnesium may mediate hip fracture risk and recovery, both of which remain largely impervious to current approaches, appears to have untapped potential for reducing the persistent global age-associated hip fracture burden and its immense associated human and social costs.

Keywords: *Bone Health; Fractures; Hip Fractures; Intervention; Magnesium; Prevention; Supplementation*

Introduction

According to Emmerson*., et al.* [1], hip fractures, which are common in the elderly population, are both painful and costly, as well as disabling, in the event the patient survives the initial traumatic event and ensuing surgery. But preventive programs that mostly focus on falls prevention, including balance and strength training, plus drug assessments and various pharmacologic and environmental management strategies are not only less than effective, despite years of efforts in this realm, but most do not commonly discuss the role of magnesium status, as a possible important nutrient determinant of bone status [2,3], as well as falls injuries, and physical activity that may influence hip fracture risk [4].

Aims of the Study

Since bone fractures, such as those that occur readily in older adults at the hip joint are affected to a considerable degree by bone mineral density, bone turnover and risk of falls and nutritional status, magnesium, and its related physiological attributes [3], this review

aimed to examine the degree of support for the idea that magnesium is a possible overlooked factor in the context of current hip fracture prevention and rehabilitation efforts [4,5]. It also aimed thereby to establish whether a need exists for more research in this realm, and if so in what regard.

Methods

To obtain the desired data to fulfill the study aims, an extensive scan of available documents housed in the PubMed, Scopus, and Web of Science Consolidated consolidated, including most full length articles published in English and derived from research conducted as of January 1980 up until October 22, 2020 using the key terms Magnesium and Hip Fractures and others outlined in table 1 were sought.

After scanning the available article listings found on these websites for potential inclusion in this current mini-review, those that addressed some aspect of the current topic of interest and were less than 10 years old, were specifically selected, downloaded and scrutinized in more depth by the author without regard to research design. After reviewing the available data, it was clear that no systematic overview of such a limited diverse data base was possible and would not be of sufficient value for definitively advancing current practice or research. Hence, while it is acknowledged that the present body of data may not be exhaustive-and that others have attempted meta-analyses or aggregate reviews on a similar theme, it was felt a more qualitative descriptive approach was the only approach that could possibly help to highlight any trends and tentative conclusions regarding this relatively uncharted topic. To this end, a narrative description of the material deemed to meet the basic review aims is presented, rather than any aggregated approach.

Results and their Analysis

General observations

As of October 22, 2020, the data examined and covering all years with no restrictions revealed only a small number of relevant studies, if compared to other themes in related research (Table 1).

Key Words	Data Base		
	Pubmed	Scopus	Web of Science
Hip Fractures	38,815	54974	68817
Magnesium	109142	303379	712689
Hip Fracture Prevention Strategies	904	760	1368
Magnesium + Osteoporosis	690	1584	1886
Magnesium + Hip Fractures	59	218	285
Magnesium + Falls Injuries	21	72	227
Magnesium Deficiency + Hip Fractures	13	50	50
Magnesium Supplementation + Hip Fractures	3	38	49

Table 1: *Summary of numbers of articles posted at key data bases as reported between January 1, 1980 - October 22, 2020 showing variations across and within databases as regards current topic and related themes.*

A further examination of the available studies revealed that regardless of data base, very few relevant clinical studies on the current topic prevail. Of these, most were housed on the PUBMED data base, despite the numbers listed above. Moreover, among the available clinical studies, very few focused studies or long term studies were observed, regardless of data base employed. In all data bases too, themes that emerged from the search were highly diverse, ranging from deficiency effects of magnesium in the context of bone health and fractures, to its possible pain-relieving and health associated anti-oxidant and cardiovascular effects, despite attempts to narrow the

topic and topic keywords. As well, additional challenges in attempts to aggregate findings in the clinical realm were numerous, including the lack of unified efforts to verify the intake of dietary sources of magnesium as discussed in some clinical studies, as well as the failure to employ similar measures of either dietary or serum levels of magnesium and/or bone mineral density measures across studies, commonly examining dissimilar samples.

However, it seems hard to refute a general consensus that magnesium, an important macro mineral and co-factor for fostering bone and muscle mass as well as neural efficacy, may be an especially important nutrient to target in efforts directed towards preventing excess bone and muscle mass loss in the elderly [4].

Research observations

Based on the belief that magnesium impacts bone, as well as general health [2] and low magnesium intake impacts bone metabolism, and possibly osteoporosis risk, Orchard*., et al.* [2] examined whether estimated magnesium intake would prove to be a possible risk factor for osteoporotic fractures and altered bone mineral density among 73,684 postmenopausal women enrolled in the Women's Health Initiative Observational Study. To this end, total daily magnesium intake was estimated from baseline food-frequency questionnaires plus supplements. Hip fractures were confirmed by a review of the subject's medical record, while other fractures were identified by self-report. Findings showed that lower magnesium intake was associated with a lower hip and whole-body bone mineral density level, but this result did not translate into increased or decreased risk of hip fractures. However, only a limited number among the cohort underwent bone mineral testing, and the study was observational and limited in duration and sample characteristics. The authors showed though that a magnesium consumption slightly greater than the recommended dietary allowance, while not increasing hip fracture risk, can increase lower-arm and wrist fractures, possibly due to its impact on fostering more physical activity and falls. Hip fractures that occurred may have been overlooked in the self-reports or follow up records, and may have been reduced in number by the favorable effects of the higher magnesium supplementation levels that were observed, but neither of these ideas could be validated.

In another magnesium-oriented study, Veronese*., et al.* [4] investigated whether 12 weeks of oral magnesium supplementation can improve the physical performance level of healthy elderly women, a potentially important factor for reducing hip fracture risk. To specifically examine this question, these researchers conducted a blinded parallel group, randomized controlled trial, of 139 healthy women, mean age: 71.5 who were attending a mild fitness program. The treatment group received 300 mg of magnesium per day, while the control group received no intervention. After assessment at baseline and again after 12 weeks, the primary outcomes in the treated group were said to be significantly better than the outcomes of the control group. These findings were more evident in participants with a magnesium dietary intake lower than the Recommended Dietary Allowance. It was concluded that daily magnesium oxide supplementation for 12 weeks can improve physical performance in healthy elderly women and might help in preventing or delaying age-related declines in physical performance, often linked to hip fracture risk.

In a related study by Genius*., et al.* [6], patients presenting to an environmental health clinic with various chronic conditions were assessed for bone health status, and those with compromised bone strength were educated about skeletal health issues and provided with therapeutic options for potential amelioration of their bone health. Patients who declined pharmacotherapy or who previously experienced failure of drug treatment were offered other options including supplemental micronutrients identified in the medical literature as sometimes having a positive impact on bone mineral density. After 12 months of consecutive supplemental micronutrient therapy with a combination that included vitamin D (3), vitamin K (2), strontium, magnesium and docosahexaenoic acid, repeat bone densitometry was performed. Results analyzed in a group of compliant patients demonstrated improved bone mineral density in patients classified with normal, osteopenia and osteoporotic bone density. According to the results, this combined micronutrient supplementation regimen appeared to be at least as effective as bisphosphonates or strontium ranelate in raising hip bone mineral density at the femoral neck and other measured bone sites. No fractures occurred in the group taking the micronutrient protocol. This micronutrient regimen also ap-

peared to show efficacy in individuals where bisphosphonate therapy was previously unsuccessful in maintaining or raising bone mineral density. Other related work, that by Farsinejad-Marj*., et al.* [7] who conducted a meta-analysis that examined magnesium effects relative to bone, indicated that high magnesium intake does not increase hip fracture risk, however, a positive marginally significant correlation was found between magnesium intake and bone mineral density in the femoral neck as well as the entire hip.

Hayhoe*., et al.* [8] similarly examined whether dietary magnesium and potassium intakes and circulating magnesium would be associated with heel bone ultrasound attenuation and osteoporotic fracture risk in a random subset of 4000 individuals from the European Perspective Investigation into Cancer and Nutrition. A cohort of 25,639 men and women with baseline data was used for bone density cross-sectional analyses and combined with fracture cases, numbering 1502, for purposes of conducting a fracture case-cohort longitudinal analyses with a mean follow-up period of 13.4 years. Relevant biological, lifestyle, and dietary covariates were then used in their regression analyses to determine associations between dietary magnesium and potassium intakes and calcaneal broadband ultrasound attenuation, as well as in Prentice-weighted Cox regression to determine associated fracture risk. Separate analyses, excluding dietary covariates, investigated associations of ultrasound records and fractures with serum magnesium concentration. The data showed statistically significant positive trends in bone attenuation measures for women, but not men across increasing quintiles of magnesium plus potassium. Reduced hip fracture risk in both men (n = 1958) and women (n = 2755) was evident for individuals in specific Mg+K (magnesium, potassium) z score intake quintiles compared with the lowest. Statistically significant trends in fracture risk in men across serum magnesium concentration groups were apparent for spine fractures and total hip, spine, and wrist fractures. None of these individual statistically significant associations remained after adjustment for multiple testing.

Groenendijk*., et al.* [9] who strove to gain insight into the nutritional status, dietary intake and muscle health of elderly Dutch hip fracture patients in efforts to prevent recurrent fractures and to underpin rehabilitation programs enrolled 40 hip fracture patients, mean age, 82 ± 8.0 years from geriatric rehabilitation wards of two nursing homes in the Netherlands into their study. Their assessments included nutritional status, dietary intake on three non-consecutive days, and handgrip strength. Muscle mass was measured using Bioelectrical Impedance Analysis and ultrasound scans of the rectus femoris. Results showed malnutrition or risk of malnutrition was present in 73% of the participants. Regarding micronutrients, the mean intakes of calcium, vitamin D, potassium, magnesium and selenium levels were significantly below those recommended. The prevalence of low muscle mass, low handgrip strength and sarcopenia were 35%, 27% and 10%, respectively, implying that a poor nutritional status, dietary intake and muscle health are common in older hip fracture patients in geriatric rehabilitation wards, and could explain their hip fracture vulnerability.

In terms of structural verification, a comparative study of hip joint replacement cases showed those with femoral neck fractures to have lower levels of magnesium, potassium, and calcium, but higher levels of sodium compared with a group of cases with degenerative changes at the hip joint [10]. The issue of a role for magnesium in the context of explaining hip fractures rates has also been raised in a population based study by Dahl., *et al* [11] who concluded drinking water with a relatively high concentration of magnesium protects against hip fractures for both men and women. In addition, hypomagnesia was cited as the reason in an early case study of bilateral spontaneous pathological fractures of the hip joint, which differentiates hip fractures from osteoarthritis [12], and a long-term prospective study has shown middle-aged Caucasian men with low serum magnesium to experience an increased risk of fractures [13]. While these data provide moderate evidence at best, a brief summary of some of these key findings shows this topic may be of considerable clinical relevance to pursue as depicted in table 2.

Researchers	Key Findings
Acosta-Olivia., *et al*. [16]	The use of magnesium sulphate in the form of intraarticular infiltration may help post operative hip fracture pain reduction
Farsinejad-Marj., *et al.* [7]	High intakes of magnesium do not appear to be associated with increased risk of hip and total fractures There is a positive albeit marginally significant correlation between magnesium intake and femoral neck bone mineral density

Genius., *et al*. [6]	A combined micronutrient supplementation regimen appears to be at least as effective as bisphosphonates or strontium ranelate in raising bone mineral density levels in hip, spine, and femoral neck sites The intake of micronutrients does not appear to produce fractures
Groenendijk., *et al*. [9]	Poor nutritional status including magnesium deficits are associated with dietary intake in general plus muscle health in older hip fracture patients in geriatric rehabilitation wards
Hayhoe., *et al.* [8]*	Dietary magnesium and potassium intakes, plus circulating magnesium are associated with heel bone ultrasound attenuation and osteoporotic fracture risk
Kunutsor., *et al*. [13]	Low serum magnesium levels and increases in rates of bone fractures are related Low serum magnesium is strongly and independently associated with an increased risk of fractures in middle-aged Caucasian men
Orchard., *et al*. [2]*	There is no selective impact of varying degrees of magnesium intake on bone mineral density levels and the relative risk of hip factures A possible detrimental effect of excess magnesium on falls and fractures other than that of the hip joint appears to prevail
Veronese., *et al.* [4]	Daily magnesium oxide supplementation for 12 weeks seemed to improve physical performance of healthy elderly women
Uwitonze., *et al*. [14]	All enzymes that metabolize vitamin D, a bone correlate, require magnesium
Welch., *et al.* [15]	Dietary magnesium may protect against adverse age associated bone changes

Table 2: *Table showing possible benefits of ensuring/attaining optimal serum and intracellular magnesium levels in efforts to ameliorate hip fracture correlates in some key studies, albeit not all*.*

Discussion

Hip fractures, an ongoing major health concern among aging populations may not only severely restrict mobility and independence but may increase the risk of premature mortality. Often associated with an elevated risk of multimorbidity, possible osteoarthritic joint changes, pain, enormous medical and social costs, and slow recovery rates in survivors, it is possible associated nutritional factors play a causative and/or mediating role in this negative cycle of health events as outlined by Capazzi*., et al.* [17] and others [18,19]. This is especially so given that pharmacologic therapies alone have not proven to date to offset falls injuries and/or ensuing hip fractures to a significant degree despite years of application and research [20]. The same applies to milk-based products, commonly thought to provide calcium and vitamin D [21].

Magnesium, on the other hand, an important mineral primarily located in bone and cartilage that impacts many physiological processes [22] and which may be deficient among older adults may be one factor that impacts hip fracture risk, through its effect on bone mineral density [23], as well as vitamin D metabolism [14,24]. Although discovered by Michaelsson*., et al.* [25] in 1995 as a possible important hip fracture determinant, the role of magnesium in this respect remains relatively unexplored, however (Table 1).

Yet, despite the paucity of data, and questionable quality of the research as a whole, it appears hard to refute the fact that a reasonably plausible case can be made for recommending that vulnerable adults, as well as aging adults might be advised to access magnesium based foods or supplements so as to try to maintain an adequate serum and intra cellular magnesium level, regardless of the lack of definitive research. Accordingly, given what we do know, magnesium may be especially helpful in improving or fostering health status, health protection, and especially bone and muscle status that impact hip fracture risk.

Indeed, although apparently increasing hip fracture risk among magnesium oxide users [26], or yielding no fracture protective effect [27] as per table 2, several related reports on this topic allude to a fairly consistent conclusion that hypomagnesium may well impact negatively on both hip fracture risk and its optimal recovery. By contrast, in addition to having a possible salient primary protection role, rehabilitation strategies to enhance functional recovery processes post hip fracture may be enhanced by the delivery of safe and recommended levels of magnesium as one component, in deficient cases [28]. The linkages between magnesium and vitamin D and bone as well as systemic health also suggests a plausible role for magnesium directly or indirectly or both in mediating hip fracture risk [29-31].

However, to more ably validate the above ideas, efforts to track the bone building and/or antioxidant properties [19], as well the pain relieving properties of magnesium [16,32] more extensive prospective studies of sufficiently long duration along with the use of bias free dietary information [33] as well as falls and fracture reports are needed to permit salient changes in these to be revealed in the context of efforts to minimize hip fracture risk and morbidity.

To this end, examining the validity of one or more of the possible linkages presented in figure 1 and as applied to carefully selected samples would possibly prove highly valuable in our view. As well, meticulously and rigorously designed studies to rule out competing hypotheses, and to avoid cross sectional inferences that do not take into account the fact that reported magnesium intake levels may not be the same as actual serum levels, and that its effects may be both disease specific, as well as dose-dependent and take weeks or months to unfold are advocated. The efficacy of tailoring doses for purposes of reducing hip fracture risk, and disability should also be examined.

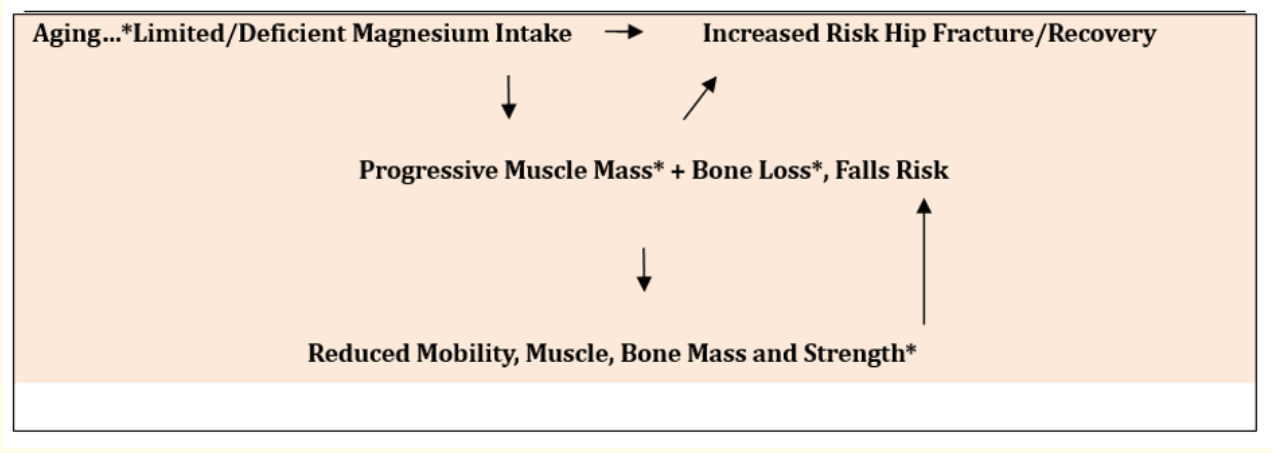

Figure 1: *Points* at which magnesium or a lack thereof may influence the hip fracture risk cycle [5,17,18].*

Conclusion

Hip fractures, which produce high levels of mortality and morbidity remain a major challenge to treat and prevent [1]. While laudable programs have been undertaken to address this issue, commonly by targeting multiple risk factors considered to heighten hip fracture risk, and with some albeit limited success, very little attention is given in this regard to the role of minerals such as magnesium, as a possible nutrient that can adversely impact hip fracture risk, if deficient. Based on this current mini-review, and in agreement with the fact that magnesium is well known for its diverse actions in promoting health [34] as well as vitamin D activation [14], and that magnesium depletion is often noted in those with chronic illnesses such as the elderly [35,40-41], it is likely that both bone mineral density as well as muscle function and physical activity while favorably affected in the presence of adequate magnesium [5,35], are less likely to be optimal in the malnourished individual, which could heighten hip fracture risk [35,39].

Moreover, even if not the key or primary nutrient explaining hip fracture risk, Yagashi [36] propose that a daily intake of magnesium in sufficient, but safe amounts, may yet be more helpful than not for minimizing bone resorption processes associated with aging, and/or for fostering vitamin D bone building actions [14], thus helping to safely reduce or minimize hip fracture risk. Due to its additional anti-oxidant and anti-inflammatory attributes, hip fracture healing may also be more likely to be favored in those older adults with adequate rather than deficient serum and intra cellular magnesium levels, as may functional recovery. While one must be mindful that some studies have reported magnesium to heighten hip fracture risk, these data, plus those that favor magnesium require replication, as well as exploration using carefully construed research approaches, regardless of study conclusion.

In the interim, since no single 'magic bullet' or 'cure' is likely to overcome the immense challenges associated with sustaining a hip fracture any time soon, sufficient cumulative evidence does appear to point to the fact that those elderly who are either at risk for frailty and osteoporosis, and are either living alone or are hospitalized with a hip fracture should undoubtedly be checked as regards their magnesium status, and treated accordingly to limit both the risk of acquiring or perpetuating a state of bone fragility and possible fracture injuries, as well as poor fracture outcomes, including possible secondary fractures. Preventive program organizers too are encouraged to not overlook the utility of ensuring their vulnerable elderly clients are able to obtain foods and/or liquids that incorporate adequate magnesium levels on a daily basis, and/or make these or supplements available, if necessary. Educators can be especially helpful in this often neglected realm in this regard by carefully expounding upon the importance of magnesium in fostering a very high number of essential physiological processes, including bone maintenance [42-45] to their high risk clients, as well as the dangers of excess intake or supplementation, and directing these older adults and their caretakers accordingly [37-40].

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