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Hypomagnesemia and Outcomes in Hematologic Malignancies

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Abstract

Magnesium, the fourth most abundant mineral in the human body, has several critically important functions in the body including cell growth, energy production and function of the immune system. There is an increasing interest in the role of magnesium in the pathology of different diseases including diabetes, cardiovascular disease and malignancies. Epidemiologic studies have demonstrated an association between a diet poor in magnesium and an increased risk of developing malignancy. Furthermore, several studies in solid malignancies have shown an association between hypomagnesemia and worse outcomes. However, there is still little known about the role of magnesium in hematologic malignancies in general. The role of magnesium in the immune system has been elucidated in patients with a rare primary immunodeficiency known as XMEN (X-linked immunodeficiency with Magnesium defect, Epstein-Barr virus (EBV) infection, and Neoplasia disease). A mutation in a gene that codes for a magnesium transporter found on T cells is responsible for impaired T cell activation and increased risk of developing hematologic malignancies. The discovery of this novel disease has increased our understanding of how magnesium may be associated with malignancies. Yet, further high-quality and well powered studies are still needed to further investigate the role of magnesium in the development of hematologic malignancies.

Keywords: Lymphoma, Magnesium, Nutrition, XMEN, Leukocyte function

Introduction

Magnesium is an essential mineral and cofactor for hundreds of enzymes and reactions. Magnesium is essential for the regulation of cell growth, division, and differentiation as well as protein synthesis, cell signaling and structural functions [1-3]. Increasing evidence in the literature suggests that low serum magnesium levels are associated with an increase in all-cause mortality in many different diseases including cardiovascular disease, osteoporosis, type 2 diabetes mellitus and hypertension [4-6]. Epidemiologic studies have demonstrated that a magnesium poor diet increases the risk of developing cancer [7,8]. Recently, hypomagnesemia has been associated with inferior survival in patients with Burkitt Lymphoma (BL) prior to undergoing chemotherapy [9]. This suggests that magnesium deficiency may play a role in hematologic malignancies. Currently, magnesium levels are not routinely checked in a new diagnosis of hematologic malignancies. The goal of this work is to stimulate studies to further investigate the role of magnesium in improving outcomes in patients with hematologic malignancies.

Importance of magnesium

Magnesium is the fourth most abundant mineral in the human body after calcium, potassium, and sodium [10]. More than 600 enzymes are activated by magnesium [11]. The total magnesium in the average adult is about 1000 mmol or around 24 grams [12]. Most of the magnesium in the human body is stored in bones, muscles and soft tissues leaving only 2% in the extracellular space [12]. 20-30% of the extracellular magnesium is bound to plasma proteins such as albumin [13]. Magnesium homeostasis is maintained by the intestines, the bones, and the kidneys [14]. Few studies have investigated the association between magnesium and albumin. Other minerals such as calcium that also are bound to albumin have a relationship

with albumin levels [15]. One older study demonstrated that albumin and magnesium concentrations are linearly related at low and high albumin concentrations. However, at normal albumin concentrations, magnesium is independent of albumin [16]. Total serum magnesium measurements may actually overestimate the incidence of hypomagnesemia when hypoalbuminemia is present and thus serum ionized magnesium may better estimate magnesium levels [17]. Contradictory to this, subsequent studies have not found these relationships to be valid [18-21]. Further studies understanding whether magnesium levels fluctuate with albumin levels are needed.

X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV), and neoplasia (XMEN) disease: A look into the role of magnesium

XMEN disease is caused by mutations in the *MAGT1* gene that codes for a magnesium transporter expressed on T cells [22]. This novel disease has allowed for a deeper understanding of the biology of magnesium and immunoregulation [23]. Magnesium influx induced by antigen receptor stimulation in T cells subsequently increases intracellular calcium concentrations which leads to T cell activation [24]. The loss of MAGT1 causes impaired T cell activation due to loss of magnesium influx [22]. T cells are essential for cytolytic control of EBV infections [25], and thus patients with XMEN disease have uncontrolled EBV infections due to impaired T cell function and increased susceptibility to EBV-associated B cell lymphomas [22]. Later studies have demonstrated that Ugandan women with low plasma magnesium levels had elevated EBV viral loads [26]. Further studies investigating the link between low serum magnesium levels, EBV viral load and the development of hematologic malignancies should be further investigated.

White blood cell dysfunction related to hypomagnesemia

Several studies have found an association between low magnesium levels and increased inflammation [3]. Studies in rats fed a magnesium deficient diet have demonstrated increased neuropeptide levels such as substance P, calcitonin gene related peptide and inflammatory markers such as IL-2, IL-4, IL-6, IL-19, and IFN-gamma [27]. Other studies in murine models have found that B-cells were decreased significantly as dietary magnesium was decreased [28]. In humans, low serum magnesium levels have been associated with elevated C-reactive protein (CRP) and IL-6 [29].

Magnesium deficiency is a contributor to chronic low-grade inflammation [27]. Chronic inflammation can suppress T-cell activation [30]. Thus, magnesium deficiency may lead to impaired lymphocyte dysfunction directly via decreased lymphocyte production and via chronic inflammation which can impair the immune system. Clearly, magnesium is essential for the proper functioning of the immune system.

Magnesium deficiency and risk of blood cancers

There are many studies linking magnesium deficiency to solid malignancies. For example, observational studies have demonstrated that increased magnesium in potable water is associated with a reduced risk of liver and esophageal cancers and decreased mortality due to breast, prostate, and ovarian cancers [31-33]. There are few studies investigating the relationship between low serum magnesium levels and hematologic malignancies, however. A higher intake of green leafy vegetables and cruciferous vegetables is associated with a lower risk of non-Hodgkins lymphoma (NHL) while an increased intake of magnesium has been inversely associated with the risk of developing diffuse large B cell lymphoma (DLBCL) [7,34]. A recent study has shown that low serum magnesium level prior to chemotherapy initiation in patients with BL is associated with poor overall survival [9]. Although this was a small retrospective study of 61 patients, it highlights the importance of obtaining a serum magnesium level as part of the workup in patients with a new diagnosis of BL. Further studies looking at whether magnesium replacement will lead to improved outcomes in patients with BL and low serum magnesium levels are needed. Additionally, more studies investigating the association of serum magnesium levels and hematologic magnesium are needed. Whether replacing magnesium will improve survival outcomes will also need to continue to be investigated.

Magnesium replacement

Dietary surveys indicate that nearly half of Americans do not consume adequate magnesium in their diet [35]. Even among Americans who use magnesium fortified foods or dietary supplementation, intake of magnesium often does not meet recommended levels [36]. There are strong reasons to encourage dietary patterns that include high magnesium foods, especially for cancer survivors. Foods that are rich in magnesium - such as whole grains, leafy greens, legumes and fish - are foods that are recommended in healthy eating patterns for cancer survivorship and prevention. Cancer research recommendations are consistent that unless a patient has an identified magnesium deficiency, magnesium should come from food sources, and not supplementation [37]. Adding a nutrient by food or medication when it is considered to be normal is referred to as supplementation while replacement is providing the element that is known

to be deficient in a patient [38]. A cancer diagnosis may be a time of opportunity for diet behavior change and is a time when patients are often seeking more information about diet [39,40]. Although this is an ideal time, little is known about the effect of dietary augmentation of magnesium in patients who are magnesium deficient. This is an area of nutrition that should be further investigated to understand the best way to replace magnesium via diet in patients who are deficient.

Ideally, magnesium would be replaced by change in the diet rather than replacement with medications. However, in patients with severe hypomagnesaemia (magnesium < 1.0 mg/dL) usually need immediate treatment with intravenous magnesium sulfate. IV administration of magnesium is inefficient and abrupt increases in serum magnesium levels can actually lead to suppression of magnesium reabsorption in the kidneys [41]. Oral magnesium replacement with oral supplements is poorly absorbed by the gastrointestinal tract (only 20-50% is absorbed) and can lead to diarrhea and gastrointestinal upset [42].

Conclusion

There are no recommendations regarding magnesium supplementation or replacement during the treatment of hematologic malignancies and there are a paucity of studies investigating whether magnesium deficiency leads to poor outcomes in these patients. Our group recently found that low magnesium levels are associated with poor outcomes in patients with BL. Based on these studies; we recommend that at least in patients with a new diagnosis of BL, a magnesium level should be checked. While it remains unclear if replacing magnesium may lead to improved outcomes, this is a potentially actionable prognostic factor in patients with hematologic malignancies. We hope to stimulate further research exploring the potential effect of hypomagnesemia on overall survival in patients with hematologic malignancies.

Product (dose)	Elemental Magnesium/Dose	Comments
Magnesium Gluconate (500 mg)	27 mg	Highest absorption among magnesium supplements [43]
Magnesium Oxide (400 mg)	242 mg	Highest amount of elemental magnesium, poorly absorbed [44]
Magnesium Hydroxide (400 mg)	167 mg	Used as a laxative, 15-30% rate of absorption [45]
Magnesium Citrate (290 mg)	48 mg	Used as a laxative, 25-30% bioavailability [46]
Magnesium Chloride (535 mg)	64 mg	Available orally and transdermally [47]

Table 1: Oral Magnesium Supplements.

Disclosure Statement

The authors report no conflict of interest.

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