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Review article

Effect of magnesium supplementation on women's health and well-being

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ABSTRACT

Magnesium is one of the most important micronutrients for the human body, is involved in many physiological pathways and is essential for the maintenance of normal cell and organ function. Magnesium deficiency in healthy individuals on a balanced diet is quite rare, but needs may change over the course of life. In women, in particular, there are various physiopathological conditions that may increase magnesium requirements, useful for both disease prevention and treatment. Indeed magnesium is well recognized in obstetrics and gynecology area. Magnesium use in women, both in terms of prevention and treatment, is extended to many health issues from PCOS to pre-menstrual syndrome, from pregnancy to menopause and beyond.

1. Introduction

Magnesium is an essential electrolyte for living organisms and is the fourth most abundant mineral in the human body, primarily found in the intracellular space (40%) or in bones and teeth (60%) [1]. This mineral, involved in more than 600 biochemical reactions in the human body, plays a key role on health and homeostasis in many ways from brain function and mood stability to bone physiology. Magnesium is important for maintaining muscle and nervous system function, cardiac electrical properties, and for supporting immune system as well as regulating glucose and insulin metabolism [2,3].

Magnesium absorption takes place mainly in the ileum and in the colon and is defined by magnesium status: the lower the magnesium level, the more the mineral is absorbed [4].

Gastrointestinal tract, bone and kidneys are the main regulators of magnesium homeostasis [4] however, despite the presence of this complex system, a number of physiological and pathological conditions may lead to magnesium deficiency among general population. Conditions such as malabsorption [5] (inflammatory bowel disease, coeliac disease, bowel resection, bariatric surgery, etc..), prolonged use of some medications (diuretics, proton pump inhibitors, antibiotics, chemotherapeutics, corticosteroids, antacids, and insulin), increased transit speed (eg. abuse of laxatives, diarrhea, vomit), excessive sweating and/or hyperhidrosis [6,7] may result in subclinical magnesium deficiency [8] and increased magnesium requirements. In addition, modification of hormonal paths regulating absorption (eg. obesity, PCOS, diabetes type II, metabolic syndrome, systemic inflammation), inadequate intake (malnutrition, restrictive or selective eating, unbalanced diets, etc.) and increased requirements (pregnancy, high physical activity, excessive sweating) are the most common causes of hypomagnesaemia [9–11].

Energy and nutrient requirements change during women's lifespan, accompanied by considerable hormonal changes, from infancy to childbearing age, climacteric period, and elderly years, in addition to pregnancy and breastfeeding that are considered distinctive life events [12]. Many women in modern society have an inadequate magnesium intake, lower than recommended, equal to 240 mg/day in adolescents and adults [13], for many reasons, including the loss of magnesium during food refining [14], with consequent subclinical magnesium deficiency (SMD).

Prevalence of SMD is between 2.5% and 15% in overall healthy women [15] and in young women (aged 18–22) with an approximately 20% incidence [16]. Besides, although the availability of many magnesium-rich foods, such as nuts, almonds, bananas, black beans, brown rice, cashews, spinach, seeds and whole grains, magnesium inadequacy and/or deficiency is relatively common, due to habitual dietary patterns rich in processed and ultra-processed foods and poor in vegetable and fruit [17,18]. It's also important to consider that the optimal dietary calcium: magnesium ratio it's close to 2 and that a ratio

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above 2:1 has been associated with increased risk of metabolic, inflammatory and cardiovascular disorder [19]. Noteworthy excessive calcium intake may negatively affect magnesium absorption, increasing magnesium requirements and leading to subclinical magnesium deficiency [20].

There is an increasing amount of evidence indicating that magnesium deficiency plays an important role in different physiological conditions occurring during women's lifespan, threatening their health and quality of life [21]. Starting from childbearing age, in which an estimated 22 million European women use oral contraceptives that have been proven to affect serum magnesium levels [22], until perimenopause, in which optimal magnesium levels have shown to help counteract disabling symptoms mainly linked to inflammatory phenomena [23]. Indeed hypomagnesaemia has been proven to contribute to oxidative stress and inflammation and to be inversely linked to C-reactive protein, an inflammatory marker [24]. Furthermore hypomagnesaemia as well as higher Ca:Mg ratio, is associated with inflammation [25] *primum movens* for many gynecological pathologies such as Polycystic Ovarian Syndrome (PCOS) or Endometriosis, and their clinical manifestations.

Magnesium homeostasis is extremely relevant to women and a growing number of studies have suggested that magnesium supplementation may represent a viable and personalized way to prevent or improve some adverse consequences of this frequently unsatisfied micronutrient requirement [26,27]. Supplements are found in the form of magnesium hydroxide [Mg(OH)2], magnesium chloride (MgCl2), magnesium citrate (C6H6O7Mg) or magnesium sulphate (MgSO4) but there is a lack in standardization parameters and guidelines for treatment, including dose, frequency and duration.

This review aims at evaluating evidences on magnesium-related health problems in women during lifespan and address suitability of magnesium supplementation.

2. Search methods

As this is a narrative review, we didn't conduct a systematic literature research. However, a MEDLINE PubMed was queried in October 2020, with no date limits, with a combination of the keywords, "Magnesium" and "women" and "supplementation". A series of hypothesis were investigated, giving priority to clinical trials published at most 10 years ago, in English language and conducted on humans. The results were screened for relevance to the review topic.

3. Childbearing age, the first stage of life

We are well aware that some dietary choices can contribute to the risk of developing hypertension, hypercholesterolemia, overweight/obesity and can compromise health [28], but a significant number of studies have recently highlighted the special role of maternal nutrition in the health of offspring [29,30]. Women of childbearing age must always maintain an adequate nutritional status precisely because they are genetically predisposed to pregnancy and must guarantee and ensure themselves and their infant health.

3.1. Premenstrual syndrome (PMS)

Women becomes fertile following menarche, which marks the beginning of this important phase of life. Unfortunately, 80–90% of women around the world suffer from PMS and 3–8% of them experience severe symptoms, defining this disorder as one of the most disabling during women's fertile life [31].

Interestingly, several studies have shown that magnesium levels in women with PMS were lower than in women without, particularly in relation to erythrocytes and leukocytes intracellular magnesium levels. Magnesium supplementation has therefore been proposed as a preventive and therapeutic approach to PMS [32,33].

Some of the risk factors for PMS, such as depressive symptoms, age and unhealthy lifestyle habits, including smoking and excessive weight gain, have also been associated with High-sensitivity C-reactive protein (hs-CRP), an acute-phase inflammatory marker [34]. Anti-inflammatory role of magnesium is well defined, so it is not surprising that several studies reported an inverse association between magnesium intake and some important inflammatory markers, including hs-CRP [35–38].

Furthermore, a recent clinical trial evaluated the role of magnesium supplementation combined with vitamin B6 for PMS treatment and this combination was found to be more effective than magnesium alone in decreasing PMS symptoms [39].

To date, there is growing evidence implicating the role of vitamin B6 in reducing inflammation, due to the hydroxyl group on 3 positions of B6 vitamers in the pyridine structure which has powerful antioxidant and anti-inflammatory action [40]. In addition, a deficiency of prostaglandin E1 (PgE1) at the central nervous system, which requires magnesium and vitamin B6 among others to be synthesized, may contribute to PMS development [41]. Finally, is important to note that an adequate intake of vitamin B6 is required for maintenance of normal intracellular magnesium concentration [42].

In the double-blinded placebo controlled clinical trial of Fathizadeh and colleagues [43], 150 women with PMS were randomly assigned to three groups: 50 women received 250 mg per day of magnesium, 50 women received 250 mg magnesium plus 40 mg vitamin B6 and 50 women received placebo. The supplementation was administered from the beginning of the menstrual cycle to the next cycle and after two months supplementation, the combination of magnesium plus vitamin B6 resulted more effective that magnesium alone and than placebo in lowering the mean PMS symptomatology score.

The same research group performed another trial on a sample of 126 women, supplementing them with magnesium and vitamin B6 from the first day of menstrual cycle until the beginning of the next cycle, with the same randomization characteristics [44]. This trial lasted 4 months and, in accordance with previous findings, the positive effects of magnesium and vitamin B6 on PMS were confirmed [44].

Reviewing different studies on the effect of magnesium on PMS, results seem to suggest that 2 months is the duration of treatment required to be effective [41], although a recent systematic review [45] recommended that further well-designed clinical trials should be performed to strengthen evidence so far gathered.

3.2. Polycystic Ovary Syndrome (PCOS)

PCOS in one of the most common endocrine disorders affecting women's fertility. The prevalence of PCOS in women of reproductive-age estimated from 5% to 18% [46,47]. PCOS is an endocrine disorder that includes clinical or biochemical hyperandrogenism, oligoanovulation and polycystic ovarian morphology, which significantly affects fertility, in addition to increasing the risk of developing metabolic syndrome, diabetes and cardiovascular diseases [48]. Disturbances in lipid and lipoprotein metabolism are common in women affected by PCOS [49] and systemic insulin resistance (IR) is likely to be at the core of the pathophysiology of this important disorder [50]. Subclinical magnesium deficiency may impair IR due to the key role magnesium (Mg) on glucose metabolism [51] suggesting a possible positive impact. Magnesium supplementation on IR of women with PCOS, being Mg involved as a cofactor in transmembrane transport of glucose and release of insulin. Noteworthy intracellular magnesium concentrations are crucial for insulin receptor phosphorylation [52,53].

In addition, magnesium supplementation combined with vitamin E, that effectively scavenges the peroxyl radical in cell membranes to inhibit lipid peroxidation, has been hypothesized to exert a synergistic effect on glycemic control [54]. In light of the synergistic effect of vitamin E and magnesium, Jamilian et colleagues [55] recently evaluated the combined approach of these molecules in a double blind randomized control trial on 60 women with PCOS, aged 18–40 years old.

The treatment group received 250 mg/day magnesium plus 400 mg/day vitamin E for 12 weeks while the control group received placebo. Women in the treatment group showed a significant reduction in serum insulin levels related to baseline measurement. Interesting, supplementation of magnesium plus vitamin E also significantly decreased serum triglycerides and VLDL-cholesterol levels [55].

Shokrpour [56] replicated this trial focusing on the effects of magnesium and vitamin E co-supplementation on hormonal status, biomarkers of inflammation and oxidative stress, assuming that oxidative stress is one of the complex mechanisms contributing to chronic inflammation and therefore leading to an increasing risk of in cardiometabolic diseases. Notably, they found a significant reduction in hirsutism and serum high-sensitivity C-reactive protein (hs-CRP) suggesting [56] that magnesium and vitamin E may improve ovarian functions by means of different prospective mechanisms, including antioxidant and anti-inflammatory action. Future studies are needed to confirm the validity of these findings at long-term in larger samples [56].

Moreover, considering inflammation, during the last decade several researches have focused on the potential synergistic effect of magnesium supplementation combined with other micronutrients with proven anti-inflammatory activity. For instance, zinc has shown effects on some inflammatory pathway probably associated with the regulation of NF-κB activation via anti-inflammatory protein A20 and peroxisome proliferator-activated receptor-α signaling [57]. In the randomized clinical trial of Afshar Ebrahimi et al. [58] 60 women affected by PCOS were assigned to either a supplement group with 250 mg of magnesium oxide plus 220 mg of zinc sulphate, containing 50 mg zinc, twice a day for 12 weeks or to a placebo group. Authors found a significant decreased serum hs-CRP and protein carbonyl (PCO) and they also observed a significant increased plasma total antioxidant capacity (TAC) level [58].

Maktabi M, et al. conducted a study aimed at investigating magnesium supplementation combined with zinc, calcium and vitamin D [59] on inflammation and oxidative stress biomarkers, in a sample of 40 women with PCOS, finding a significant reduction in hirsutism, serum hs-CRP, and plasma malondialdehyde, with a significant increase in plasma total antioxidant capacity concentration [59]. According to this trial, the treatment group received 100 mg magnesium, 4 mg zinc, 400 mg calcium plus 200 IU vitamin D twice a day for 12 weeks, versus control group receiving placebo [59].

It's well known that increased levels of hs-CRP are associated with hyperinsulinemia, insulin resistance and adiposity in women affected by PCOS, and taken individually all the components of this co-supplementation provide anti-inflammatory actions. In addition, previous studies demonstrated that increased inflammatory cytokines play an important role also in insulin resistance [60,61].

PCOS is clearly one of the obesity-related condition but also exist mechanisms whereby the development of PCOS can lead to further weight-gain, contribute to obesity development [62]. The co-occurrence of obesity with PCOS and the association with cardiometabolic dysfunction and insulin resistance justify this close link between obesity and PCOS [63] In addition, several studies have identified and association between obesity and magnesium deficiency and increase consumption of fast food and decreased intake of fibers, whole grains, and green leafy vegetables is associated with both obesity and hypomagnesemia [64–66]. Both conditions exacerbate a pro-oxidant and pro-inflammatory state and magnesium supplementation seems to be an alternative adjuvant in the management of metabolic health, particularly on inflammatory indexes reduction. Several cohort studies showed an inverse association between dietary magnesium intake and cardiovascular disease risk [67,68], but results concerning magnesium supplementation are still inconsistent.

Magensium supplementation could be useful for several conditions related to inflammation but there is a lot of heterogeneity related to the bioavailability of the magnesium salt to be used, duration of treatment, and how to assess magnesium status of the target population [69].

3.3. Pregnancy

In the routine gynecological practice, magnesium play a well recognized role both in treatment and prevention. First of all, it should be considered that magnesium deficiency may have influence on epigenetic changes leading to cardiac and vascular muscle phenotype alterations increasing risk of non communicable diseases and other vessel related symptoms and diseases [70]. Magneisum deficiency is associated with uterine hyperexcitability, preterm labour and intrauterine growth retardation [71].

Along this line, several studies have found that magnesium supplementation decreases the risk of one of the most common causes of maternal and fetal morbidity and mortality: preeclampsia [72,73].

Preeclampsia is characterized by increased metabolism and a state of inflammation in the placenta and blood vessels with endothelial and vascular dysfunction which could lead to preterm labour [74]. Magnesium deficiency has been established to play a role in blood pressure regulation and hence the development of preeclampsia [75]. Pregnancy-induced hypertension is characterized by elevated blood pressure and increased neuromuscular irritability and these symptoms are also attributable to magnesium deficiency in non-pregnant women [76].

Magnesium has demonstrated superiority over both placebo and other antiepileptics in its ability to prevent eclampsia in preeclamptic women [77].

In addition, a recent study on 102 pregnant women found a statistically significant negative association between preeclampsia and both serum magnesium before 20 weeks of pregnancy and serum magnesium at term [70], suggesting a causative role of magnesium deficiency in the development of preeclampsia and emphasizing the fundamental role of the nutritional status in pregnancy.

This results indicated that checking magnesium level should be considered as the predicting factor of preeclampsia during the first evaluation of pregnancy [78,79].

A recent systematic review also support an inverse association between serum magnesium levels and rates of preterm birth [80].

Further studies are required to better understand the mechanism of action and validate these hypotheses.

4. Climacteric and menopause, the second stage of life

The fertility cycle ends with menopause, which begins when the menstrual cycle finishes and is a transition into a new phase of women's life.

During this period women experience climateric symptoms, including vasomotor ones, changes in mood, sleep disturbances, etc.… which may significantly impair quality of life [81–83]. Those symptoms largely depend on the decline in circulating endogenous oestrogens, but recent evidence suggested a role of magnesium supplementation in reducing the duration and intensity of those unpleasant manifestations, as well as typical risk factors.

It's worth to notice that an inverse association between dietary magnesium intake and the risk of depression was recently found in a representative sample of the general population, 17,730 adults from the 2007–2014 National Health and Nutrition Examination Survey [84]. During an observational study on postmenopausal women Authors observed the lowest magnesium levels in women with depressive symptoms and the highest in women without depressive symptom, indicating higher vulnerability to depression in women with inadequate magnesium level [85]. To reinforce this hypothesis, a recent systematic review [86] provided evidence of magnesium involvement in mood disorders highlighting that magnesium supplementation was associated with a decline in depressive symptoms. Future studies should aim to reduce confounding and measurement errors in order to increase strength of evidence.

4.1. Bone health

Low serum magnesium has been demonstrated to be associated with low bone density both in pre and postmenopausal women [87] and evidence shows lower magnesium levels in osteoporotic postmenopausal women compared with non-osteoporotic ones [88].

Furthermore, it is known that dietary intake of magnesium has a beneficial role in inflammation and oxidative stress, both risk factors for osteoporosis: it is therefore reasonable to assume a protective effect of magnesium on conceivable osteoporotic fractures [89–92].

In the last decade, only one trial by Aydin et al. [93] evaluated magnesium supplementation on bone reabsorption markers in 30 postmenopausal osteoporotic women. Half of them received a daily oral dose of 1830 mg magnesium citrate for 30 days while the other half received placebo. This study showed that magnesium supplementation suppressed bone turnover. Particularly, oral magnesium supplementation led to a significant reduction in urinary deoxypyridinoline levels and to a significant increase in osteocalcin level [93].

Furthermore, magnesium plays another critical role in the prevention of osteoporosis: it's well recognized that insufficient Vitamin D levels contribute to the onset of osteoporosis through reduced calcium absorption [94] and Vitamin D nutritional status is accurately represented by serum 25-hydroxyvitamin D (25(OH)D) level [95].Both in vitro and in vivo studies have indicated that magnesium deficiency affects 1α-hydroxylase (i.e., CYP27B1) and 24-hydroxylase (i.e., CYP24A1), which synthesizes and metabolizes 25(OH)D and 1,25(OH)2D, respectively [96–98]. Findings from a recent clinical trial suggested that optimal magnesium status may be important for optimizing 25-hydroxyvitamin D status [99]. This study included 180 subjects aged 40–85 y who were randomly assigned to receive a customized dose of magnesium glycinate supplementation that would reduce the calcium-to-magnesium intake ratio to ~2.3 based on their baseline calcium and magnesium intakes, according to previous result [100,101].

4.2. Cardiovascular risk

4.2.1. Hot flashes

Another common symptom of menopause and peri-menopause is hot flashes, which are uncomfortable and have also recently been supposed to be associated with adverse cardiovascular risk factor profile, including elevated blood pressure, higher blood lipids and insulin resistance [102]. It's well known that magnesium has been used in cardiovascular disorders treatment and prevention and that this mineral plays a pivotal role in the regulation of blood pressure, insulin metabolism and cardiac excitability [103].

In addition, hot flashes are mediated by an imbalance in serotonin and norepinephrine in the brain that causes vasomotor instability and magnesium is known to be neuroactive, vasoactive, affecting serotonin in many body cells, including brain. Evidence suggests that magnesium is likely to be a reasonable causal link between vasomotor symptoms and menopause [104,105].

Two recent and consecutive trials tested magnesium supplementation in reducing hot flashes in menopausal women with a history of breast cancer, taking into consideration that hot flashes are commonly experienced during chemotherapy [107].

In the pilot phase trial on 25 subjects were supplemented with magnesium oxide 400 mg for 4 weeks, 56% of women had a >50% reduction in hot flash score (frequency × severity). Results from this trial allowed to plan a double-blind, placebo-controlled randomized trial with a sample size of 289 postmenopausal women with a past diagnosis of breast cancer [107]. Subjects were randomly assigned into three groups: one received 1200 mg of daily magnesium oxide, the other one received a daily dose of 800 mg magnesium oxide and the last group received placebo. At the end of 8 weeks trial period, serum magnesium levels were unchanged after treatment with magnesium, and supplementation failed to improve hot flash scores, concluding that further studies are needed to better define role, timing, dosage and kind of magnesium supplementation in these patients.

4.2.2. Hypertension

After menopause, the prevalence of hypertension in women rises due to different mechanisms in aging compared with men [108].

Hypertension is a major risk factor for cardiovascular disease in women at this stage of life [109] and evidence shows that blood pressure may be well less controlled in women then in men [110].

Several studies support a positive relationship between menopause and hypertension [111,112] especially in women reporting vasomotor symptoms with a greater risk of hypertension [113].

The role of magnesium deficiency in the development of hypertension is well supported [114,115] but to date, findings on the relationship between magnesium supplementation and blood pressure are inconsistent. A recent meta-analysis [116] has highlighted a statistically significant inverse relationship between dietary magnesium intake and hypertension risk, despite no association between the risk of hypertension and per-unit increment of serum magnesium concentration was found.

Moreover, recent data showed evidence that a combined deficiency in magnesium and vitamin D is detected in essential hypertension [117,118] and may be of special pathogenetic importance, especially in patients with diabetes mellitus type IIb in which decreased magnesium concentrations and vitamin D levels are related to increased interleukin levels that are complicit in the development of arterial stiffness and arteriosclerosis. Evidence suggests that both magnesium and vitamin D in hypertensive patients with diabetes mellitus type IIb should be carefully considered and eventually corrected immediately [119].

Ana Rosa Cunha [120] and colleagues carried out a double-blind randomized clinical trial on 35 women with uncontrolled hypertension treated with diuretics, aged 40–65 years, in order to evaluate the effect of magnesium supplementation on functional vascular changes and blood pressure control. Subjects were randomized to receive oral 600 mg of magnesium chelate twice a day for 6 months or placebo. Finally, supplementation was associated with a better blood pressure control, improved endothelial function and enhanced of subclinical atherosclerosis.

Risk factors for hypertension also include obesity; many women report gaining weight as they transit through menopause [121] and this could be one of the contributors to hypertension development. In the second Nurses' Health Study [122] authors found that the strongest risk factor for developing hypertension was an increased body mass index (BMI) and obese women had 4.7 times higher incidence of hypertension than women with BMI < 23.0 kg/m2. In this study, 40% of new hypertension cases were attributed to overweight or obesity.

Moreover at this age, there's an increase of weight-promoting drugs prescription, which establish a vicious circle increasing both risk of NCDs as well as risk of micronutrient inadequacies, [123] including magnesium, which is already pretty common in western population despite the apparent good health status [124].

Nevertheless, a recent meta-analysis [125] aimed at evaluating the effects of magnesium supplementation on blood pressure and obesity among patients with type IIb diabetes mellitus found that magnesium supplementation had beneficial effects on blood pressure regardless of body weight status.

There is currently evidence suggesting beneficial effects of magnesium supplementation in menopausal women, but extensive studies are needed to establish treatment characteristics, taking into account lifestyle and medications use.

5. Conclusion

Magnesium is an essential mineral that plays a pivotal role in many physiological functions and it is involved in numerous enzymatic reactions. Magnesium supplementation has been used successfully in the

treatment of different conditions such as PMS, PCOS, mood disorders, and postmenopausal symptoms and consequent risk factors, particularly in the association with other dietary components with proven antioxidant and anti-inflammatory activity.

Women's nutritional needs change in response to physiological modifications throughout lifespan, lower magnesium levels may be common throughout women's lives and are associated with adverse health outcomes and reduced quality of life. However, individual needs change according to lifestyle and health status, besides personal factors, including phenotyping and genetic predisposition, and this suggest that inter- and intra-individual differences, should be considered for effective prevention delivering personalized nutrition. Important information as the ones measurable by "omics" tools, and related analytical techniques, associated to individual's phenotypic, medical, lifestyle characteristics as well as eating habits and behaviors, will result into specific dietary interventions, nutritional guidance and tailored supplementation prescription in terms of requirements, dose and duration.

Availability of data and materials

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Author contributions

HC and DP conceived the presented review; DP, AL and LB provided literature research, DP wrote the manuscript with support from HC. HC and HKB supervised the findings of this work. All authors discussed the results and contributed to the final manuscript. All author approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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