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Menopausal hot flashes: The role of magnesium and select endocrine factors

Maya Orlofsky, Serin Seckin* and Ozgul Muneyyirci-Delale

Department of Obstetrics and Gynecology, SUNY Downstate Medical Center, Brooklyn, NY 11203, USA

Abstract

Hot flashes are a highly prevalent and distressing symptom experienced in menopause, but very little is known about their pathogenesis. Hypomagnesemia may be involved in menopausal hot flashes, but there is a dearth of research in this area. Certain hormones such as insulin, ghrelin, and melatonin, as well as adipokine factors, may also be involved.

A systematic search was conducted using key words including menopause, hot flashes, vasomotor symptoms, ionized magnesium, ionized calcium to magnesium ratio, insulin resistance, adipokine and ghrelin levels, and melatonin. Articles were included if they used human subjects, female subjects, and were published in English. Articles were excluded if they were published prior to the year 1990, if they were review articles, or if the article was not relevant to the current review.

691 articles were found and, after exclusion of studies based on the above criteria, 17 articles were included in the review. 8,667 patients were collectively represented. Magnesium supplementation for hot flashes demonstrated mixed results, with one study showing improvement of symptoms and another study showing no significant improvement. Hypomagnesemia and hot flashes were separately found to be associated with increased insulin resistance, increased adipokine levels, and increased ghrelin levels. Melatonin supplementation was not found to improve hot flash symptoms.

Few studies have directly researched the relationship between magnesium and menopausal hot flashes, and the results have been inconclusive. Stronger relationships have been found between hot flashes and increased insulin resistance, adipokine, and ghrelin levels. Further research is needed, as these findings may indicate future novel treatment options for menopausal hot flashes.

Introduction

Hot flashes are one of the most common complaints in menopause, with up to 79% of women experiencing hot flashes by completion of the menopausal transition [1]. They can have significant effects on quality of life; links have been demonstrated between hot flashes and depressed mood, sleep disturbances, cardiovascular health, and bone health [2].

One area of research that has not been extensively studied is that of the role of ionized magnesium (Mg^{2+}) in the physiology of menopausal hot flashes. Magnesium is a cofactor in over 600 known enzymatic reactions in the body, with ionized magnesium (Mg^{2+}) as the most biologically active form [3]. Low ionized magnesium levels have been demonstrated in patients with chronic renal failure, asthma, pre-eclampsia, and patients hospitalized in the intensive care unit [4-7]. Hypomagnesemia in menopause may lead to deleterious effects throughout the body. Menopausal women with hypomagnesemia were found to have increased thyroid-stimulating hormone (TSH), which could lead to clinical hypothyroidism [8]. Magnesium has been found to be involved in serotonin and norepinephrine transmission, and therefore hypomagnesemia may be involved in depression, a common comorbidity of menopause. Magnesium may additionally reduce adrenocorticotropic hormone (ACTH) activity, thus hypomagnesemia may cause an increased release of cortisol in response to stress [9]. Magnesium has also been shown to increase the synthesis of nitric oxide, an important vasodilator [10].

In this literature review, the hypothesis that hypomagnesemia as well as altered levels of other endocrine factors are involved in the pathophysiology of menopausal hot flashes will be investigated.

Our focus lies mainly on magnesium. However, due to the dearth of studies on its role in hot flashes, this review was expanded to include other endocrine factors with which magnesium is known to have an association, such as insulin, adipokines, ghrelin, and melatonin.

Materials and methods

In conducting this literature review, systematic online searches were conducted by two separate reviewers through PubMed, MEDLINE, and Google Scholar. Additionally, the textbook "Clinical Gynecologic Endocrinology and Infertility" was used as a reference [11]. Search terms included "menopause and magnesium", "hot flashes and magnesium", "vasomotor symptoms and magnesium", "ionized magnesium and menopause", "ionized calcium to magnesium ratio and menopause", "insulin resistance and magnesium", "insulin resistance and hot flashes", "adipokines and magnesium", "adipokines and hot flashes", "ghrelin and magnesium", "ghrelin and hot flashes", "melatonin and magnesium", and "melatonin and hot flashes". Articles were included if they used human subjects, female subjects, and were published in English. Articles were excluded if they were published prior to the year 1990, if they were review articles, or if the article was not relevant to the current review. Quality of the evidence was assessed using the scheme set by the Oxford

***Correspondence to:** Dr. Serin Seckin, M.D., 450 Clarkson Avenue, Department of OB/GYN, Brooklyn, NY 11203, USA, E-mail: serin.i.seckin@gmail.com

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Centre for Evidence-Based Medicine, with 1 being the highest quality and 5 being the lowest quality [12].

Results

In total, 691 articles were found, 674 were excluded based on the above criteria, and the following 17 articles were reviewed. These 17 studies included 4 randomized control trials, 1 non-randomized control trial, 2 prospective cohort studies, 5 prospective case-control studies, 1 two-part prospective case-control and cross-sectional study, and 4 cross-sectional studies. In total, 8667 patients were collectively represented by these studies. The following sections are titled by the keywords used in each search.

1. Menopause, magnesium, ionized magnesium, ionized calcium to magnesium ratio

In this search, only one prospective study by Muneyirci-Delale et al. was found (Table 1). This study looked at ionized magnesium levels and the ionized calcium to magnesium ratio in menopausal and pre-menopausal women. Pre-menopausal women were evaluated in both follicular and ovulatory phases. Menopausal women had higher magnesium and calcium levels compared to pre-menopausal women. Magnesium levels inversely correlated with estrogen levels in both pre-menopausal and menopausal women. The ionized calcium to magnesium ratio increased as estrogen increased but was not found to be elevated in either pre-menopausal or menopausal women [13].

2. Hot flashes and magnesium

In this search, two studies from the Park et al. [14] group were examined, in which patients experiencing hot flashes were given

supplemental magnesium (Table 2). In the phase II trial (n = 25), treatment with 400-800 mg of magnesium oxide was successful in reducing hot flashes. The larger randomized control study (n = 289) using treatment with 800 or 1200 mg of magnesium oxide yielded some improvement in symptoms, with 1200 mg doses being slightly more effective, but this improvement was not significant in comparison to placebo [15].

3. Magnesium, insulin resistance, menopause, and hot flashes

In this search, 8 studies were found (Table 3). Four of these studies examined the relationship between hypomagnesemia and type 2 diabetes. Lower magnesium levels in diabetic patients were demonstrated in two studies, with one prospective study specifically assessing ionized magnesium [16,17]. Lecube et al. [18] similarly found in a two-part cross-sectional and prospective study that as diabetes resolved in obese patients after bariatric surgery, their magnesium levels increased [18]. Another randomized control study demonstrated that magnesium supplementation improved the glycemic status of prediabetic patients [19]. Two studies were found that examined magnesium levels and insulin resistance. One prospective study showed that patients with lower ionized magnesium levels showed decreased insulin sensitivity [20]. Another group used the homeostasis model assessment of insulin resistance (HOMA-IR) to show that obese women with lower intracellular magnesium levels had increased insulin resistance in a prospective study [21]. Finally, two studies specifically assessed insulin resistance in menopause. A smaller prospective study by Tuomikoski et al. [22] (n = 131) found no association between insulin resistance and hot flashes, although insulin resistance did negatively correlate with estradiol levels. A larger longitudinal cohort study using

Table 1. Menopause, magnesium, ionized magnesium, ionized calcium to magnesium ratio

Author(s)	Year Published	Study Type	Quality Rating	Summary of Findings
Muneyirci-Delale O, et al. [13]	1999	Prospective case-control study	3	In menopausal women, magnesium levels inversely correlated with estrogen, serum calcium levels were elevated, and the ionized calcium to magnesium ratio was not elevated.

Table 2. Hot flashes and magnesium

Author(s)	Year Published	Study Type	Quality Rating	Summary of Findings
Park H, et al. [14]	2011	Pilot phase II non-randomized clinical trial	2	Breast cancer patients with hot flashes were successfully treated with magnesium.
Park H, et al. [15]	2015	Double-blinded randomized-control trial	1	Breast cancer patients with hot flashes were treated with magnesium but did not have significant improvement.

Table 3. Magnesium, insulin resistance, menopause, and hot flashes

Author(s)	Year Published	Study Type	Quality Rating	Summary of Findings
Resnick LM, et al. [17]	1993	Prospective case-control study	3	Type 2 diabetic patients were found to have lower levels of serum ionized magnesium and intracellular free magnesium than non-diabetic controls.
Barbagallo M, et al. [20]	1997	Prospective case-control study	3	Hypertensive subjects were found to have lower basal ionized magnesium levels, which correlated with lower cellular responsiveness to insulin.
Lecube A, et al. [18]	2012	Cross-sectional case-control study and prospective case-control study	4; 3	Obese subjects that underwent bariatric surgery and whose diabetes subsequently resolved had increases in magnesium levels.
Tuomikoski P, et al. [22]	2012	Prospective case-control study	3	Menopausal women were found to have no association between hot flashes and insulin levels, glucose levels, or insulin resistance. Insulin resistance was found to have a negative correlation with estradiol levels.
Thurston R, et al. [23]	2012	Prospective longitudinal cohort study	2	Participants in SWAN cohort with hot flashes had associated increased insulin resistance.
Cruz K, et al. [21]	2014	Prospective case-control study	3	Obese women were found to have a negative correlation between erythrocyte magnesium and insulin resistance.
Guerrero-Romero F, et al. [19]	2015	Double-blinded randomized-control trial	1	Prediabetic patients with hypomagnesemia had reduced plasma glucose and improved glycemic status after being given magnesium supplementation.
Wei J, et al. [16]	2016	Cross-sectional study	4	Serum magnesium was found to be inversely correlated with diabetes in a Chinese population, but dietary magnesium was not significantly correlated.

Table 4. Hot flashes, adipokine, and ghrelin levels

Author(s)	Year Published	Study Type	Quality Rating	Summary of Findings
Alexander C, <i>et al.</i> [24]	2010	Cross-sectional study	4	Midlife, premenopausal women were found to have positive correlations between leptin levels and hot flash occurrence and duration.
Thurston R, <i>et al.</i> [25]	2013	Prospective longitudinal cohort study	2	Participants in SWAN cohort with adverse adipokine profiles had more hot flashes.
Huang, WY, <i>et al.</i> [26]	2017	Cross-sectional study	4	Women who experienced hot flashes had higher levels of adipokines and higher insulin resistance.
Karim R, <i>et al.</i> [27]	2020	Post-hoc cross-sectional study using data from two clinical trials	4	Menopausal women with hot flashes were found to have higher levels of ghrelin, but leptin, adiponectin, and resistin levels were not associated.

Table 5. Hot flashes and melatonin

Author(s)	Year Published	Study Type	Quality Rating	Summary of Findings
Secreto G, <i>et al.</i> [28]	2004	Double-blinded randomized-control trial	1	Treatment of menopausal women with melatonin did not show any advantage in relief of symptoms in comparison to placebo.
Chen WY, <i>et al.</i> [29]	2014	Randomized control trial	1	Melatonin supplementation in menopausal breast cancer survivors was associated with increased subjective sleep quality in comparison to placebo, but no significant change in hot flash symptoms.

data from the Study of Women's Health Across the Nation (SWAN) ($n = 3075$) found conflicting results, with a significant association between insulin resistance and menopausal hot flashes [23].

4. Hot flashes, adipokine, and ghrelin levels

In this search, 4 studies were found (Table 4). Two of these studies showed higher leptin levels in women experiencing hot flashes, whether or not they had reached menopausal status; one cross-sectional study analyzed a group of premenopausal women ($n = 211$) and one longitudinal cohort study assessed a group of women early in their menopausal transition ($n = 536$) [24,25]. Huang *et al.* [26] found in a cross-sectional study ($n = 151$) that not only did women with hot flashes have higher leptin levels, but also increased insulin resistance using the HOMA-IR. Finally, a recent cross-sectional study ($n = 898$) discovered that women with hot flashes who were menopausal did not have increased leptin levels, in contrast to the previous study, but did have increased ghrelin levels [27].

5. Hot flashes and melatonin

In this search, 2 studies were found (Table 5). Both randomized control studies evaluated the effect of supplementation of melatonin on menopausal hot flashes, and both studies found that there was no significant relief of symptoms with this treatment. Women with menopausal hot flashes were found to have increased sleep quality with melatonin treatment by Chen *et al.* [28,29].

Pathophysiology

The physiological mechanism behind hot flashes is not completely understood. It is thought that an increase in hypothalamic thermosensitivity narrows the range within which the hypothalamus perceives as normal core temperature, causing a lowering of the sweat threshold and elevation of the shivering threshold. Thus, small increases in body temperature will trigger a supernormal heat dissipation response, including peripheral vasodilation and sweating, manifested as a hot flash [30]. Sex hormones are likely involved in the pathogenesis of hot flashes as lower levels of estrogen have been observed in women experiencing menopausal hot flashes [31]. However, hot flashes are not experienced in prepubertal females who also have low levels of estrogen. Thus, exposure to adult levels of estrogen and then subsequent withdrawal may be more crucial to the formation of vasomotor symptoms than hypoestrogenism itself [32]. A study in rats found that estradiol may act on the ventromedial nucleus of the hypothalamus to inhibit thermogenesis and decrease energy expenditure. Therefore,

it is possible that in an estrogen-depleted state core temperature can become dysregulated [33].

Other hormones may also play a role: higher follicle-stimulating hormone (FSH) concentrations have been shown to be associated with increased hot flash symptoms [34]. Pulsatile release of luteinizing hormone (LH) was found to be synchronized with the onset of hot flashes, and more recently it was discovered that neurons co-expressing kisspeptin, neurokinin B, and dynorphin (KNDy neurons) are involved in both generating LH pulses and thermoregulation. These are thermoregulatory neurons found in the arcuate nucleus of the hypothalamus that express estrogen receptors and become hypertrophied in the absence of estrogen, and therefore may be of relevance in the development of hot flashes in the estrogen-depleted state of menopause [35-37].

Obesity is strongly associated with hot flashes. Increased levels of adipose tissue were previously thought to be protective against hot flashes due to increased androgen aromatization to estrogens in said tissue, but it appears the opposite is true [2]. Levels of adipokines - signaling proteins that are secreted from adipose tissue - have been found to increase during menopause and may be involved in the pathogenesis of hot flashes. This may further explain why obesity is a major risk factor for hot flashes [24,38]. Other risk factors for hot flashes include smoking, African-American ethnicity, lower socioeconomic status, history of depression or anxiety, and history of experiencing child abuse [2,39].

Neurotransmitters may also be involved. Melatonin levels were found to be decreased during menopause, which may be related to the increased nocturnal awakenings associated with hot flashes [40]. Norepinephrine metabolite levels were shown to be increased before and during hot flashes [41]. Conversely, administration of clonidine, an α_2 -adrenergic agonist, has been demonstrated to provide relief of hot flashes [42]. Decreased estrogen also correlates with decreased serotonin levels and upregulation of hypothalamic serotonin receptors, some of which may be involved in heat loss mechanisms [43,44]. These findings are consistent with the idea that hot flashes are mediated centrally.

Clinical presentation

Typical symptoms experienced during a hot flash include a sudden feeling of heat in the chest and face that then spreads throughout the body, as well as sweating and palpitations. This lasts for a few minutes and can then be followed by chills and shivering [2]. Hot flashes are also associated with increased nocturnal awakening [45].

Assessment and diagnosis

The diagnosis of hot flashes is usually clinical, but there are also measurement techniques for hot flashes as well. Subjective measurements of hot flashes can be done by questionnaires that assess for factors such as frequency, severity, and associated symptoms. Objective measurements of hot flashes include analysis of sternal skin conductance and sweat levels via hot flash monitors [46].

Treatment

Current pharmacologic treatments include hormone therapy, such as estrogen therapy, as well as antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), clonidine, and gabapentin [47]. Continuous transdermal nitroglycerin is a new experimental treatment for hot flashes that works by tolerance-induced suppression of nitric oxide-mediated vasodilation [48]. Treatments that target the KNDy system are also currently being studied [49,50]. Some women are unable to use hormone therapy as treatment due to contraindications to exogenous estrogen, such as those with a history of breast cancer, therefore it is important to study other possible treatments for hot flashes [51].

Prognosis

Symptoms of hot flashes may persist frequently for over seven years, as was demonstrated by the SWAN study. Hot flashes were reported for about 4.5 years after patients' final menstrual period [52].

Discussion

After reviewing the current literature, it appears there is some evidence that supports the hypothesis of hypomagnesemia involvement in the pathophysiology of menopausal hot flashes. Only one study by Muneyyirci-Delale O *et al.* was found to evaluate the levels of ionized magnesium (Mg^{2+}) in menopausal women, and hot flash experience was not assessed. Mg^{2+} was found to increase with the menopausal decrease in estrogen, which was theorized to be protective, as higher Mg^{2+} facilitates lower blood pressure and lower peripheral resistance, effects that would have previously been carried out by estrogen. This may be necessary due to increased cardiovascular contractility in menopause due to increased calcium ions (Ca^{2+}) from increased bone metabolism [13]. Thus, it appears that magnesium levels change with menopause, but it is not clear if this is related to hot flashes. Two studies were found in which women with hot flashes were given supplemental magnesium with conflicting results [14,15]. A later review pointed out, though, that only women with hot flashes induced by breast cancer pharmacotherapy were evaluated, rather than those with age-related menopause [53]. Furthermore, these trials did not assess whether hypomagnesemia was involved in the development of hot flashes, nor did they specifically measure ionized magnesium (Mg^{2+}) levels. It is difficult to assess magnesium activity because most magnesium is intracellular, so erythrocyte intracellular magnesium levels is a target that perhaps should be additionally measured [54].

Another similar area of interest within hot flash physiology is that of the ionized calcium to magnesium ratio ($Ca^{2+}:Mg^{2+}$). As previously stated, Ca^{2+} and Mg^{2+} levels are known to rise in menopause [13]. Increases in $Ca^{2+}:Mg^{2+}$, however, have been associated with vasospasm, a major risk factor in strokes, hypertension, pre-eclampsia, asthma, and sickle cell anemia [5-7,55,56]. Muneyyirci-Delale O *et al.* also assessed this ratio in menopausal women and it was not found to be elevated. It was theorized that this is protective, as described above [13]. However, menopausal hot flashes may be due to hypomagnesemia, and therefore

it would follow that these women have higher $Ca^{2+}:Mg^{2+}$. Women with hot flashes may then be at risk for conditions related to vasospasm, but further investigation is needed. As mentioned earlier, hot flashes have been found to be associated with cardiovascular disease and dysfunction [57,58].

Certain endocrine factors, including insulin, adipokines, ghrelin, and melatonin, may also be involved in the pathogenesis of menopausal hot flashes, which is the latter portion of our hypothesis in this review. This association was supported by many of the reviewed articles. In addition, many of these hormones and factors were found to also have a relationship with magnesium, suggesting an interplay between these pathways.

Multiple studies in this review showed that diabetic subjects were found to have significantly lower levels of serum magnesium than nondiabetic controls, and intracellular magnesium was found to inversely correlate with glycemic control [16,18,21]. Magnesium supplementation has also been found to potentially reduce insulin resistance [19,59]. Increased levels of insulin also appear to increase renal magnesium excretion. Thus, insulin resistance and type 2 diabetes may precipitate the development of hypomagnesemia [60]. This potentially underlies an older hypothesis that obesity was associated with hypomagnesemia, but it may be due to the common comorbidity of diabetes [18]. Since hypomagnesemia may also be involved in hot flashes, menopausal women experiencing hot flashes may be at risk for increased insulin resistance, and vice versa. However, one study that examined this potential relationship between menopause and diabetes risk found no significant association [61]. Two studies found in this review examined the relationship between hot flashes and insulin resistance with conflicting results, possibly due to a difference in sample size [22,23]. Interestingly, kisspeptin levels have been found to inversely correlate with insulin secretion, and therefore the increased kisspeptin levels seen in menopause may cause decreased insulin levels [62]. Additionally, decreased levels of nitric oxide were found to cause increased insulin clearance [63].

Adipokines, such as leptin, adiponectin, and resistin, as well as the related gastric hormone ghrelin, were investigated for their possible role in the pathogenesis of hot flashes. Higher leptin levels were found to be correlated with worse experiences of hot flashes in three of the four studies reviewed [24-26]. Karim *et al.* [27] did not find a correlation between leptin levels and hot flash intensity, but they attributed that to their cohort being relatively older. Animal studies have found leptin to be involved in hypothalamic thermoregulation and energy expenditure [64,65]. Leptin levels are increased in people with higher amounts of adipose tissue, which may be part of why hot flashes are associated with obesity [25]. Other adipokines have also been investigated. Low adiponectin was found to be associated with hot flashes, but resistin levels had no significant association [25,26]. A study in mice showed that adiponectin may have an inverse relationship with body temperature [66]. In the study of older menopausal women, ghrelin was also found to be increased with hot flashes. It was theorized that ghrelin may play a role in hypothalamic thermoregulation via modulation of KNDy neurons [27]. Interestingly, one study found that leptin and adiponectin were also associated with increased insulin resistance in menopausal women [26].

Finally, we investigated if melatonin played a role in menopausal hot flashes. It has been well-established that menopause is associated with changes in sleep, especially insomnia [67]. Hot flashes are a significant cause of sleep impairment in menopause, and low melatonin levels have been found in menopausal women as well.^{40,55} Therefore, it is

possible that there is a relationship between the two. The studies found in this review, however, showed no significant improvement of hot flash symptoms in menopausal women treated with melatonin. Interestingly, magnesium has been found to improve sleep disturbances in elderly patients [68,69]. In another study, women were found to have decreased daytime sleepiness after magnesium supplementation [70]. It may be that hypomagnesemia is involved in sleep disturbance in menopausal hot flashes.

In summary, more research is needed in the pathophysiology of menopausal hot flashes, as well as the potential involvement of magnesium and other endocrine factors. To the best of the authors' knowledge, this is the only review that has investigated and consolidated all these potential contributing factors to present a novel view of the mechanisms underlying menopausal hot flashes.

Limitations

The major limitation of this literature review is there were very few articles on the topic of menopausal hot flashes and magnesium. Additionally, the only databases used to find articles were PubMed, MEDLINE, and Google Scholar. Finally, the exclusionary criteria applied to the searches also limited the research highlighted in this paper.

Future directions

There are multiple future directions for research in the topic of menopause and magnesium. First, a study specifically examining the relationship between low levels of magnesium, especially ionized magnesium, and menopausal hot flashes, has not been done. The relationship between hot flashes and the ionized calcium to magnesium ratio has also not been well established. Additionally, the correlations of magnesium and hot flashes to insulin resistance, adipokines, ghrelin, and melatonin have not been thoroughly researched.

Conclusion

In summary, the relationship between menopausal hot flashes and hypomagnesemia is significantly understudied and warrants further investigation. Few studies discussed in this literature review directly investigated the role of magnesium in hot flashes, and ionized magnesium was rarely measured. However, multiple studies showed that hypomagnesemia and hot flashes separately had similar correlations with insulin resistance, adipokine, and ghrelin levels, thus a relationship between these pathways should be researched further. Future studies may greatly benefit from assessing levels of ionized magnesium to better understand the activity of magnesium in the body and how magnesium is involved in menopausal hot flashes.

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Conflicts of interest

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Ethical approval

IRB reviewed and determined to not be human subject's research.

Author contributions

MO: literature review and analysis, drafting of manuscript, preparation of tables, submission of manuscript.

SS: literature review and analysis, drafting of manuscript.

OMD: oversight and design of literature review and analysis, editing of manuscript.

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