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Research Article

A Randomized, Double-Blind, Placebo-Controlled, Comparator Trial Evaluating Magtein® Magnesium Supplement on Quality of Life as Related to Levels of Stress, Anxiety, Fear and Other Indicators

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Received: January 27, 2022; **Published:** February 25, 2022

Abstract

Introduction: Low magnesium levels have been implicated in the pathophysiology of stress, anxiety, depression, and other quality of life measure. Magnesium supplements in general are thought to be poorly absorbed and further not to influence brain magnesium levels. Magtein® magnesium has been shown to enhance magnesium levels, RBC magnesium, and brain magnesium levels in rodents and humans.

Objective: To determine if supplementation with magnesium L-threonate (Magtein®) improves anxiety/stress and fear in healthy adults.

Methods: A randomized, double-blind, placebo-controlled, parallel-designed study was conducted in adults aged 50 - 70 years with self-reported complaints of stress and anxiety that perceptually impacted quality of life. This study evaluated Magtein® magnesium vs placebo on anxiety and anxiety-related emotions using the Hamilton Anxiety Rating Scale (HAM-A and likert scales). Subjects were given ~25 mg/kg/day of magnesium L-threonate (Magtein®) or placebo for 12 weeks. Subjects between 50 and 70 kg took 1.5 g/day, subjects between 70 and 100 kg took 2 g/day.

Results: HAM-A total (total anxiety score) and the subcategories of Mood and Tension, for both Magtein® and placebo groups showed significant improvement at week 6 and week 12, with no differences between groups. The Magtein group had significantly greater improvements in Likert scored stress anxiety levels compared to baseline. Additionally, the Magtein® group demonstrated significant reduction in the fear subset of the HAM-A at weeks six and 12, while the placebo group stayed the same. The differences between groups did not reach significance.

Conclusion: The group receiving Magtein® significantly improved their perceived stress and anxiety levels, while also experiencing significant and clinically meaningful reduction in HAM-A scored fear. More research is warranted to evaluate the positive quality of life impacts Magtein® appears to have in this study population.

Keywords: *Magnesium; Magnesium L-Threonate; Stress; Anxiety; Quality of Life*

Abbreviations

Mg: Magnesium; NHANES: National Health and Nutrition Examination Survey; HPAA: Hypothalamic Pituitary Adrenal Axis; CSF: Cerebrospinal Fluid; L-TAMS (Formerly MgT): L-Threonic Acid Magnesium Salt; MMSE: Mini-Mental State Examination Score; PSQI: Pittsburgh Sleep Quality Index; HAM-A: Hamilton Anxiety Questionnaire-A; ANCOVA: Analysis of Covariance; NMDA: N-Methyl-D-Aspartate

Introduction

Magnesium (Mg) is an abundant mineral used as a cofactor for over 300 metabolic reactions. These include energy production, protein synthesis, DNA and RNA synthesis, mitochondrial function, and many more. Mg is needed for maintaining normal nerve and muscle function, heart rhythm, neuromuscular conduction, muscular contraction, vasomotor tone, normal blood pressure, bone integrity, and glucose and insulin metabolism [1]. While overt deficiencies are rare, data from the National Health and Nutrition Examination Survey (NHANES) of 2013 - 2016 found that 48% of Americans of all ages ingest less Mg from food and beverages than is recommended [2]. It has been suggested that the lower intake may be related to many chronic diseases particularly those connected with chronic inflammation such as obesity, hypertension, type 2 diabetes, and atherosclerosis [3]. Mg supplementation has been shown to improve symptoms of migraine headaches, Alzheimer's disease, stroke, hypertension, cardiovascular disease, and type 2 diabetes mellitus [4]. A recent systematic review of 18 studies suggested that Mg supplementation had a beneficial effect on subjective anxiety in subjects prone to anxiety though the quality of the evidence was indicated as poor [5]. Another systematic review of 21 studies reported that a higher intake of Mg was associated with lower depression symptoms [6]. Mg has been shown to play a role in the pathophysiology of depression by impacting the functioning of the limbic-hypothalamus-pituitary adrenocortical axis [7], as well as other key pathways identified as playing a role in depression [5]. Supplementation of 450 mg of elemental Mg for 12 weeks has been shown to be as effective in reducing depression symptoms as a tricyclic antidepressant (Imipramine 50 mg) in depressed hypomnesia elderly patients with type II diabetes [8]. A relationship between Mg and anxiety has also been identified. For example, test anxiety, related to exposure to stressful exam conditions, increases urinary Mg excretion, resulting in a partial reduction of serum Mg levels [9]. This is supported by evidence that demonstrates the role of Mg in the stress response showing that Mg helps attenuate the response to a stressor via the hypothalamic-pituitary-adrenal axis (HPAA) [10]. Mg is found in a variety of foods, including whole grains, spinach, nuts, legumes, and potatoes [1]. Despite the abundance of Mg in the food supply, almost half of the population consumes less than the recommended amounts [2]. Considering this widespread inadequate intake combined with the key physiological functions Mg plays a role in, supplementation may be warranted. However, many of the commercially available Mg supplements have poor bioavailability and do not result in elevation of brain Mg [11]. Typically, in humans, increasing blood Mg by up to 300% only changes cerebrospinal fluid (CSF) Mg by less than 19% [12]. To overcome this problem, L-Threonic acid Magnesium salt (L-TAMS, formerly MgT), a compound that can effectively enhance CSF Mg concentration via oral intake was developed and has been validated to elevate brain levels of Mg and well as raise circulating levels of Mg [11]. In addition, in animal models of fear and taste aversion, Magtein® intake has been shown to improve animals' responses to control fear and unpleasant taste [13-16]. A previous publication of data from this same study demonstrated significant elevation of brain magnesium levels as well as improvement in cognitive abilities in the supplemented group as compared to the placebo [17].

Purpose of the Study

The purpose of this study to examine the effects of Magtein® on stress, anxiety, and and quality off life indication in this group of participants. This manuscript contains previously unreported data from a prior published study on this form of magnesium [17].

Materials and Methods

Study design

This was a 12-week randomized, double-blind, placebo-controlled study evaluating magnesium L-threonate (Magtein®) as compared to Placebo.

Participants

Subjects were men or women aged 50 and 70 years without diagnosed psychological disorders, but with self-reported complaints of cognition (memory and concentration), anxiety, and sleep issues. The inclusion and exclusion criteria were described in detail in a previous publication [17]. In brief, to be included in the study subjects scored equal to or greater than 24 on the Mini-Mental State Examination score (MMSE) to rule out dementia and Alzheimer's disease. They reported sleep difficulties defined by a score of greater than 5 on the Pittsburgh Sleep Quality Index (PSQI) and demonstrated the presence of mild-to-moderate anxiety, with scores ≥ 12 and ≤ 28 on the Hamilton Anxiety Questionnaire-A (HAM-A).

Subjects were asked to stop taking any dietary supplements at least 7 days prior to randomization and during the study. They refrained from alcohol consumption or exercise for at least 24 hours prior to each test visit. Subjects were asked to maintain their standard and normal diet and dietary habits. Dietary magnesium intake was assessed as part of the screening criteria. Whole blood magnesium values were collected as part of this study and have been previously reported [17].

Recruitment and randomization

A total of 51 subjects (age 50 - 70) were recruited and were randomly assigned to the Magtein® or placebo group in a ratio of 1:1, using a block-2 randomization schedule. Subjects received a sequential number corresponding to the order in which they entered the study. Study sponsors, investigators, research coordinators, attending care teams, and subjects were blinded to treatment groups. The subjects were provided with the study product at the second visit and were asked to bring the unused product to each follow-up visit so that compliance with product administration instructions could be determined. Blood was collected at each visit to assess efficacy and ensure subject safety. The study was executed by Miami Research Associates (Miami, FL) with review and approval by Aspire IRB (Santee, CA).

Dosage

Dosage was set to correspond to approximately 25 mg/kg/day. To accomplish this, subjects between 50 and 70 kg took 1.5 g/day (containing about 108 mg of elemental magnesium), and subjects between 70 and 100 kg took 2 g/day of Magtein® (containing about 144 mg of elemental magnesium). At the end of the study, 8 subjects (35%) were taking 1.5g of Magtein® per day, and 15 subjects (65%) were taking 2g of Magtein® per day.

Assessment of anxiety and stress

Subjective and objective evaluation of anxiety and related conditions was measured by the HAM-A and a Likert Stress/Anxiety questionnaire. For the HAM-A, total score and sub-scores (anxious mood, tension, fears, insomnia, and intellectual) were utilized in the study with only the data for total score; anxiety and fear reported here. Though reported elsewhere, quality of sleep was measured by the PSQI. Cognitive abilities were measured by the Eriksen flanker task, digit-span task, Trail Making Test (Parts A and B), and the cued name recall task (includes the face-name association task) (Data previously published) [17].

The HAM-A, a rating scale used in both clinical and research settings to measure the severity of anxiety symptoms, consists of 14 items, each defined by a series of symptoms, designed to measure both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The HAM-A does not provide any standardized probe questions and is administered by a clinician (subject does not complete the questionnaire his/herself). Each item is scored on a scale of 0 (not present) to 4 (severe) with a total score range of 0 to 56 where < 17 indicates mild severity, 18 to 24 indicates mild to moderate severity, and 25 to 30 indicates moderate to severe severity. The HAM-A were performed at visit 1 to determine eligibility and as a baseline reading (scores ≥ 12 and ≤ 28 were considered inclusive) and at visits 3 and 4 the HAM-A was used to help determine product efficacy.

For the subjective rating of stress and anxiety, subjects were asked to rate their feelings regarding the products' effects on perceived stress and anxiety (Likert Scale). Subjects were asked: "On a scale of 1 to 5, how do you feel that taking the supplement helped to reduce your perceived stress or anxiety?" with answers as follows: 1: no difference, 2: may be slightly improved, 3: slightly improved, 4: moderately improved and 5: significantly improved. The questionnaires were performed at visits 3 and 4.

Statistical analysis

Enrollment for this study was targeted at 50 subjects (25 per group). Based on a previous internal small group open-label trial, the analysis was powered by noting a 50% reduction in HAM-A scores would be considered clinically meaningful. Assuming a serial coefficient correlation of about 0.5 for HAM-A scores at baseline and 12 weeks, the within-group SD of the 12-week changes would also be ± 10 score points. Using an unpaired Student t-test with a significance level of 0.05, a total enrollment of 50 subjects (40 completers if 20% attrition) was required for the study to be able to detect differences of about a 45% reduction in HAM-A score. We assumed an attrition rate of 20% based on the previous experience of the contract research organization.

Only data from subjects that completed all visits were included in the statistical analysis (per protocol analysis); therefore, there were no missing data values in the dataset.

The mean change from baseline to each subsequent time point was tested for nominal significance by the paired Student t-test, or by the non-parametric Wilcoxon test if non-normally distributed. For each continuous variable at each time point, the mean differences in the variable, or in the change in that variable from baseline, between active and placebo products was tested for nominal significance by the paired Student t-test or by the nonparametric Wilcoxon test if non-normally distributed. For each categorical variable, difference in the distribution of categories between the different product groups was tested for nominal significance by the Fisher Exact test if possible, or by the Chi-Square test if necessary. Within product group and differences in these changes between products, we also conducted a formal efficacy test, using an analysis of covariance (ANCOVA), where the value of the variable at the end of the study is the dependent variable, the supplement or placebo is the main factor, and the value of the variable at baseline is a covariate. The coefficient of the supplement (relative to placebo) and its standard error of estimate was calculated from the ANCOVA.

Results

Out of the 51 participants enrolled in the study, 25 subjects received Magtein® and 26 received placebo. Two subjects (14%) discontinued the study prematurely in the Magtein® group and 5 in the placebo group. The remaining 44 subjects completed the study and were included in the efficacy per-protocol analysis.

In total score of HAM-A as well as in subcategories of Mood and Tension, both Magtein® and placebo groups showed significant improvement at week 6 as well as week 12 ($p < 0.001$, respectively), with no between-group difference.

In the HAM-A subcategory of Fear, the placebo group showed no change or improvement from baseline at both week 6 ($p = 0.379$) as well as week 12 ($p = 0.110$), while Magtein® showed significant decreases from baseline in the Fear sub-score at both weeks 6 and 12 ($p = 0.002$, $p = 0.018$, respectively). The magnitude of reduction from baseline to weeks 6 and 12 for the HAM-A fear was also considered clinically meaningful (> 50% change), while the Placebo group did not achieve these same outcomes. The differences between groups did not reach statistical significance, however, the change score did meet the definition of meaningful change (Figure 1).

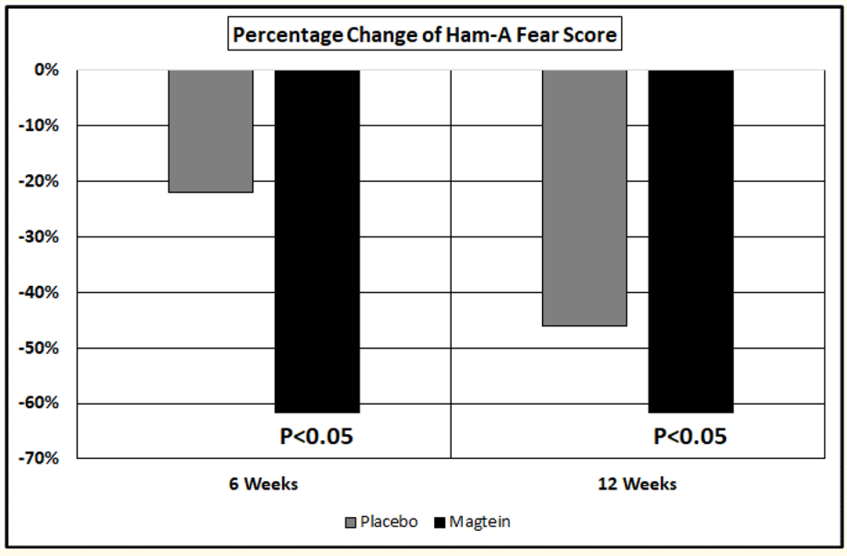

Figure 1: *Change from baseline in HAM-A score.*

In addition to HAM-A questionnaires, subjects were asked to rate their feelings (Likert Scale) regarding the products' effects on perceived stress and anxiety at week 6 as well as week 12 visits. From week 6 to week 12, the group receiving Magtein® showed significant improvement from baseline in stress/anxiety ($p = 0.005$), while the placebo group did not have significant changes during the same period of time ($p = 0.288$), there was no significant difference between groups (See figure 2).

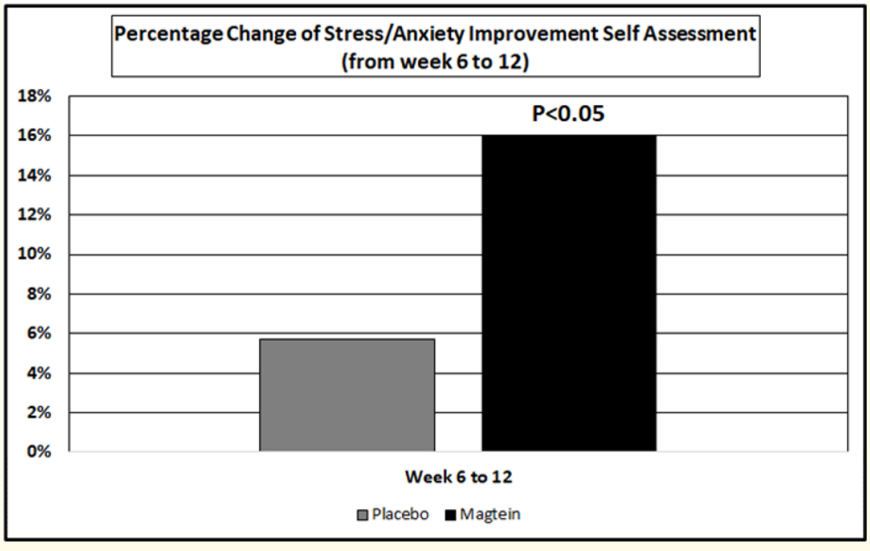

Figure 2: *Change from baseline in stress/anxiety measures.*

Discussion

Mg plays a key role in the activity of psycho-neuroendocrine systems. Depletion and supplementation studies in animals and humans suggest that Magnesium may play an important part in the etiology of stress/anxiety, depression, and mood dysfunctions [6,18-20].

In this study, we found that total score of HAM-A as well as in subcategories of Mood and Tension, both Magtein® and placebo groups showed significant improvement at week 6 as well as week 12, with no between-group difference. In the subcategory of fear, the placebo group showed no significant improvement from baseline at both week 6 as well as week 12, while Magtein® showed significant decreases from baseline in the Fear sub-score at weeks 6 and 12. The differences between groups did not reach significance. Our findings are supported by evidence that Mg levels are significantly correlated with anxiety-related behavior in animal models [21]. Additionally, studies have shown that supplementing Mg levels in mice has been demonstrated to reduce the expression of anxiety-related behavior [19,22]. A relationship between Mg status and anxiety is also evident in humans [9,23]. Mg intake was shown to be inversely associated with subjective anxiety in a large community-based survey [24]. Furthermore, Mg supplementation has been shown to attenuate the activity of the stress response via the HPAA [25,26]. Therefore, it is plausible that Mg influences anxiety states via the moderation of the stress response.

Several molecular mechanisms have been proposed to explain the relationship between Mg and anxiety. It has been suggested that glutamate, the primary excitatory neurotransmitter in the mammalian brain, acts on N-methyl-D-aspartate (NMDA) ionotropic receptors which have been implicated in anxiety and panic disorders [27]. Furthermore, Mg is a natural blocker of NMDA receptor [28]. Mg is also essential for the activity of mGluRs, the G-protein coupled receptors that are widely expressed in the brain [29,30] which play a key modulatory role in glutamatergic activity, secretion and presynaptic release of glutamate, activity of the GABAergic system, and regulation of the neuroendocrine system. The action of glutamate on mGluRs receptors has been implicated in responses to fear, anxiety, and panic [30]. Mg may additionally balance the over activation of glutamate via increasing GABAergic availability. An imbalance between GABA and glutamate was shown to be associated with anxiety disorders [31].

An important factor that influences the effectiveness of Mg on stress/anxiety management is the bioavailability of different Mg forms, especially the effect of these magnesium forms on Mg levels in the brain, where psychological functions are controlled. Magnesium chloride, sulphate, citrate, lactate, malate, glycinate, and taurinate are examples of higher bioavailable Mg forms as compared to Mg oxide, but bioavailability is limited [32-34]. Magnesium L threonate (Magtein®), a novel magnesium preparation developed by MIT lab [11] has demonstrated potential as a magnesium preparation that can elevate brain Mg via chronic oral supplementation. A previous publication of a double-blind, placebo-controlled human clinical examining the effects of Magtein® in older participants demonstrated significant elevation of brain Mg levels as well as cognitive abilities in supplemented group as compared to the placebo [17]. It is interesting to note that the effective elemental magnesium levels used for the observed benefits of Magnesium L threonate (Magtein®) were 108-144 mg/day which is below the RDA of 350 - 420 mg/day.

The limitations of this study include the small sample size (n = 51) at one clinic site which limits diversity of the subjects tested and thus limits generalizing the results. Furthermore, the subjects were healthy with self-reported anxiety therefore there is no way of knowing the clinical significance of the results and whether those with diagnosed conditions would experience the same results. In addition, the length of supplementation was short, a longer supplementation period may reveal different outcomes. The strengths of the study include a well-controlled design and statistical analysis. Future studies should consider a larger sample size of subjects so that more definitive conclusions can be made regarding the potential for this specific magnesium supplement to impact quality of life as related to managing stress, anxiety, and other aspects surrounding quality of life.

Conclusion

This randomized, double-blind, placebo-controlled trial demonstrated that those receiving the dietary supplement Magtein® experienced a significant and meaningful improvement in HAM-A Fear score when compared to baseline. In addition, the Magtein® group

achieved significant improvement in self-rated stress and anxiety levels over the course of the study, whereas the Placebo group did not. Further research assessing the potential benefit of Magtein® magnesium for quality of life as related to anxiety and stress is warranted.

Acknowledgements

We would like to thank Jennifer Gu, PhD of AIDP Inc. for her contributions to the writing of this manuscript.

Conflict of Interest

This study was sponsored by AIDP Inc. AIDP commissioned GRAS Associates/Nutrasource as a third party to write this manuscript. The study was carried out by Miami Research Associates/QPS. At the time the manuscript was written the authors were employed by GRAS Associates/Nutrasource but independently interpreted the data and authored the manuscript.

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