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PARKINSON'S DISEASE

ABSTRACT & COMMENTARY

Mindfulness Yoga for Managing Psychological Symptoms of Parkinson's Disease

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Dr. Feldman reports no financial relationships relevant to this field of study.

SOURCE: Kwok JYY, Kwan JCY, Auyeung M, et al. Effects of mindfulness yoga vs stretching and resistance training exercises on anxiety and depression for people with Parkinson disease: A randomized clinical trial. *JAMA Neurol* 2019;76:755-763.

SYNOPSIS: A mindfulness yoga program was more effective than stretching and resistance training in addressing the symptoms of depression and anxiety in patients with mild to moderate Parkinson's disease; both interventions showed equal efficacy in improving symptoms related to motor impairment.

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured." – James Parkinson, 1817

In the early 1800s, surgeon James Parkinson identified a cluster of patients with distinct appearance and motor impairment, but likely did not envision that one day his name would be attached to this neurological condition. It was not until the mid- to late 1800s that neurologist Jean-Martin Charcot, when describing cardinal features of the disorder, separated it from other known neurological conditions, and coined the term "Parkinson's Disorder" to describe this set of patients typically presenting with bradykinesia, tremor, rigidity, and postural instability.[1,2]

Early treatment efforts aimed to ameliorate these motor symptoms via both pharmacologic and nonpharmacologic interventions. In the mid-1900s,

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Summary Points

- The goal of this single-blind, randomized study was to compare a mindfulness yoga program developed for Parkinson's patients to conventional stretching and resistance training exercises in treatment of specific psychological and motor symptoms in patients with mild to moderate Parkinson's disease.
- Symptoms of anxiety and depression, measures related to mobility, severity of motor symptoms, and health-related quality of life were assessed at baseline, eight weeks, and 20 weeks in 138 patients with mild to moderate Parkinson's disease.
- Participants in the mindfulness yoga program arm of the study had significant improvement in anxiety and depression measurements at both time points compared to participants in the stretching and resistance training exercises arm.
- Measures of motor functioning and mobility improved for both groups equally.

medical science grew to understand the important role of dopamine in Parkinson's disease (PD). By 1970, the use of high doses of levodopa (l-dopa) showed dramatic effects in addressing the motoric manifestations of PD. However, the progressive deterioration associated with this disorder continued, albeit at a slower pace.[1,2]

More recently, attention has shifted to nonmotor psychological symptoms of PD and the role these play in functional impairment and reduced quality of life (QOL). Up to 40% of patients with PD experience symptoms of anxiety disorders (including generalized anxiety disorder and panic disorder), and just under 20% experience a form of depression. Medication use and effectiveness is limited, in part because of side effects of these agents that worsen the motor manifestations of PD. Anxiety is thought to be critical to address since it can directly worsen some of the motor symptoms of PD, such as tremors and gait problems, as well as nonmotor symptoms, such as dysphagia, sleep disturbance, and cognitive impairment.[3,4]

Kwok et al noted the importance of managing psychological symptoms in patients with PD and theorized that a complementary approach could bypass the negative side effects seen with available pharmacologic agents. Additionally, the team noted that stretching and resistance training exercises (SRTE) are recommended for management of PD motor symptoms and that mind-body exercise, including yoga, tai chi, and dance, has documented evidence of effectiveness in controlling these symptoms. The premise of the Kwok et al study is that a program incorporating mindful movement, breathing exercises, and meditation could address both the motor and psychological symptoms of PD, leading to increased QOL. A mindfulness yoga program for PD (MY-PD) incorporating these elements was developed and compared to SRTE in this Hong Kong-based, assessor-blinded study.

MY-PD is a 90-minute program composed of 15 minutes of breathing exercises, 15 minutes of warm-up, 30 minutes of progressive Hatha yoga poses, 15 minutes of controlled breathing, and 15 minutes of meditation.

Participants with a diagnosis of mild to moderate PD who had the cognitive ability to participate in a full exercise and mindfulness program were recruited from regional neurology clinics. Exclusions included treatment for a psychiatric disorder. The investigators randomized 138 eligible participants to receive either 90 minutes of MY-PD weekly for eight weeks or 60 minutes of SRTE weekly over this same period. All participants were asked to practice at home as well.

Changes in anxiety and depressive symptoms, measured using the Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire, are shown in Table 1. The HADS has subscales for

Table 1: Changes in Anxiety and Depression for Treatment Groups (SRTE vs. MY-PD)

	Baseline*		Week 8*		Week 20*	
	SRTE	MY-PD	SRTE	MY-PD	SRTE	MY-PD
HADS (anxiety subscale)	5.66	6.32	5.22	3.97 *P* = 0.001	4.95	3.04 ***P* < 0.001**
HADS (depression subscale)	6.16	6.69	5.9	4.10 ***P* < 0.001**	6.00	3.53 ***P* < 0.001**
Movement disorders (United Parkinson Disease Rating Scale)	31.64	34.90	22.53	21.10 *P* = 0.001	23.25	22.14 *P* = 0.002
Timed Up & Go (TUG) test	14.05	17.54	12.41	14.72 *P* = 0.72	13.47	12.36 *P* = 0.99
Holistic well-being scale: Perceived hardship	3.88	4.04	4.02	3.22 ***P* < 0.001**	3.89	3.13 ***P* < 0.001**
Holistic well-being scale: Perceived equanimity	6.82	6.47	7.58	6.78 ***P* < 0.001**	7.60	6.57 ***P* < 0.001**

SRTE: Stretching and resistance training; MY-PD: mindfulness-based yoga developed for Parkinson's disease (PD); HADS: Hospital Anxiety and Depression Scale.
P values shown in the chart reflect results of the MY-PD arm compared with the SRTE arm. Significant results are noted in bold.
*All scores represent mean scores.

anxiety and depression; on each subscale, higher scores indicate higher severity of symptoms. The minimal clinically significant difference in scores is 1.32 on HADS anxiety and 1.40 on HADS depression subscales; clinically relevant cut-off for diagnosis is a subscore of 8 (out of 28).

Notably, there was equivalent improvement in motor functioning and mobility at week 8 (end of each exercise program) and week 20 with each intervention. However, there were significant differences in improvement in measures of symptoms of anxiety, depression, and overall QOL in the participants undergoing MY-PD at most time points. The only exception was that at week 8, there was a nonsignificant improvement in anxiety symptoms among those in the MY-PD arm. By week 20, the improvement was statistically significant.

Additional measurements included severity of motor movements, mobility, spiritual well-being, and health-related QOL (HRQOL). Some adverse effects were reported. Several participants from each group reported temporary knee pain, but none required further medical intervention.

■ COMMENTARY

PD ranks second to Alzheimer's disease as the most common neurodegenerative disease. In the United States, there are estimates that 60,000 new cases of PD are diagnosed each year, that about 1 million persons are currently diagnosed with PD, and that the direct and indirect economic impact of this disorder is greater than $20 billion annually. Although medication and even surgical interventions are helpful in controlling the motor impairments of PD, reducing the burden of the psychological nonmotor symptoms remains an elusive, under-investigated goal. As control of these nonmotor symptoms can be key to maintaining function and preventing out-of-home placement, addressing this issue with robust and sound medical studies is critical.[3,4,5]

Kwok et al added an important study to the field with this randomized, controlled trial of MY-PD vs. SRTE. Interestingly, both interventions consist of multiple elements. MY-PD combines mindfulness, yoga, and breathing exercises while SRTE combines stretching and resistance training. Although the combinations make practical sense, unfortunately this makes it more difficult to draw conclusions about efficacy. Future investigations most likely will need to address this issue by isolating and evaluating effectiveness of exercise program components.

A recently published comprehensive review of nonpharmacologic interventions to manage anxiety in PD explored this issue.[6] This study reviewed 13 investigations of various quality and noted that a common element was the use of breath in a focused manner. They recommended looking at the "feasibility of using focused breathing, alone, as an intervention for the self-management of anxiety in Parkinson's disease."[6]

This recommendation is useful to keep in mind when reviewing the Kwok et al study, as focused breathing

certainly is a major component of MY-PD. However, there is little necessity to wait for future investigations to recommend mindfulness-based yoga to patients with PD, especially since the motor improvements seen with MY-PD and SRTE were equivalent and the MY-PD arm demonstrated the added advantage of significant improvement in psychological symptoms.

One drawback to recommending this approach globally is that the research is not broad-based enough to generalize this approach for all patients with PD. There are several aspects of the research to keep in mind. First, it is important to remember that these authors looked for improvement in anxiety and depression symptoms, and that none of the groups showed a mean HADS score of clinically diagnosable levels for either of these disorders at baseline. This implies that while participants had symptoms of anxiety and depression, full criteria for a diagnosis were absent. It may be that those with more severe disease were not eligible for the study. Regardless, these results do not give information regarding the treatment of full-blown anxiety or depression with either intervention. Second, it is equally useful to note that the authors only looked at participants with mild to moderate PD; there is not enough information to extrapolate recommendations for treatment of patients with more severe PD.

Considering these limitations, the Kwok et al study certainly provides evidence for use of mindfulness-based yoga in patients with mild to moderate PD, especially for patients who have symptoms of anxiety and depression. While availability of such a program may be a limiting factor, the providers still can encourage patients and families to look for mindfulness-based interventions and discuss adoption of mindfulness techniques with physical therapists or others working with patients with PD. Furthermore, this study reminds providers and patients of the critical importance of a holistic approach to treatment of PD and the need to address both motor and nonmotor symptoms in a comprehensive treatment plan. ■

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TINNITUS

ABSTRACT & COMMENTARY

Ginkgo Benefits for Tinnitus?

By David Kiefer, MD, Editor

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Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: Twelve weeks of twice-daily *Ginkgo biloba* extract improved symptoms as effectively as pentoxifylline in 200 adults with chronic tinnitus.

SOURCE: Procházková K, Šejna I, Skutil J, et al. *Ginkgo biloba* extract EGb 761® versus pentoxifylline in chronic tinnitus: A randomized, double-blind clinical trial. *Int J Clin Pharm* 2018;40:1335-1341.

Tinnitus, or ringing in the ears, is a symptom that can be acute or chronic and have numerous etiologies.[1] It is notoriously difficult to treat, with some of the options including noise masking, pharmaceuticals (tricyclic antidepressants, selective serotonin reuptake inhibitors, pentoxifylline, steroids, etc.), acupuncture, and cognitive behavioral therapy. Integrative modalities (including herbal medicine) step into the void of consistently effective therapies. One of the botanicals most evaluated for tinnitus is ginkgo (*Ginkgo biloba*, Family Ginkgoaceae). Procházková et al pitted ginkgo vs. one pharmaceutical option, pentoxifylline, both of which are thought to increase cochlear and cerebral blood flow.

The researchers recruited people with chronic tinnitus from an ear, nose, and throat clinic in the Czech Republic. Inclusion criteria are detailed in Table 1.

Summary Points

- For 12 weeks, 200 study participants with chronic tinnitus received either 120 mg of *Ginkgo biloba* (extract EGB761®) or 600 mg pentoxifylline twice daily. There was no placebo group.
- Daily ratings for tinnitus loudness and annoyance were collected and analyzed.
- Both treatment groups similarly improved during the course of the study in a variety of parameters.
- In the ginkgo group, anxiety and depression scales statistically improved more than in the pentoxifylline group.

Exclusion criteria included tinnitus from pharmaceuticals, any current tinnitus treatment, and a variety of severe medical conditions.

Study participants were randomized to receive, twice daily, either one 120 mg tablet of the standardized *G. biloba* extract EGB761® and a placebo tablet meant to look like pentoxifylline, or a 600 mg tablet of pentoxifylline and a placebo tablet meant to look like EGB761. EGB761 is an extract that has been subject to numerous clinical trials for a variety of medical conditions, and is standardized to 22-27% flavone glycosides and 5-7% terpene lactones, two of the groups of phytochemicals thought to provide ginkgo's physiologic effects. Both participants and study personnel were blind to the groups' allocation and treatments received.

Daily, study participants rated the tinnitus loudness (from 0 "no tinnitus" to 10 "extremely loud") and annoyance (from 0 "not annoying at all" to 10 "unbearably annoying"); these were the primary outcomes. Participants completed several other questionnaires at the beginning and end of the 12-week period: the abridged Tinnitus Questionnaire (Mini-TQ), a 12-item scale designed to capture some of the psychological distress associated with tinnitus; the Hospital Anxiety and Depression Scale (HADS), which analyzes symptoms as the name implies; and the Sheeham Disability Scale (SDS), used to measure how psychological symptoms affect a person's life.

A total of 200 people were randomized, with 100 in each group. Seven of the ginkgo group stopped their therapy, and 17 of the pentoxifylline group dropped out. One ginkgo participant and two pentoxifylline participants were not analyzed because there were no data post-baseline. Demographics and baseline scores were similar between the two groups pre-intervention. Of note, all study participants were white, the average age was 54 years, and the majority (59%) were women.

Table 1: Inclusion Criteria

- At least 30 years of age
- Tinnitus of at least three months' duration
- Tinnitus able to be masked by noise
- A score of at least a 3 (out of 11) of noise annoyance
- A score of at least a 5 on the abridged Tinnitus Questionnaire (Mini-TQ)
- Gave informed consent

The results, shown in Table 2, revealed no difference between the two treatment groups, and both groups improved over the three months. Weekly median scores in the various scales used were statistically analyzed to show these changes. The authors did subgroup analyses of the participants based on their HADS depression and anxiety scores. For those participants with a baseline HADS depression score ≥ 8 (indicating subclinical or clinical depression), there was a statistically significant improvement in Mini-TQ, loudness, and annoyance after 12 weeks that was not seen in the pentoxifylline group. Similarly, there were some participants with abnormal HADS anxiety scores at baseline (34 in the ginkgo group, 29 in the pentoxifylline group). After 12 weeks, fewer people in the ginkgo group remained with clinical anxiety than in the pentoxifylline group (n = 22, P = 0.005 vs. n = 26, P = 0.105).

Adverse effects occurred more in the pentoxifylline group (27 participants, 36 adverse events) than in the ginkgo group (19 participants, 20 adverse events). The most common adverse effects were gastrointestinal (n = 11 in the pentoxifylline group) and worsening of tinnitus (n = 5 in the ginkgo group).

■ COMMENTARY

This study seems to add a tool to the tinnitus treatment toolbox. Compared to a pharmaceutical, a commonly used and studied formulation of *G. biloba* leaf fared as well in several parameters meant to follow the symptoms of tinnitus and its effects on peoples' mental health and lives in general. Particularly interesting is the possible advantage of ginkgo over pentoxifylline in terms of benefit and safety. With respect to benefit, that subset of patients with pre-existing anxiety or depression did fare better with ginkgo, and ginkgo seemed to be better tolerated overall. These are important findings, especially as clinicians help patients negotiate the risk-benefit decision-making

Table 2: Ginkgo vs. Pentoxifylline Score Changes After 12 Weeks		
Screening	**Ginkgo**	**Pentoxifylline**
Mini-TQ	-1.57	-1.94
Loudness (11-point)	-0.41	-0.43
Annoyance (11-point)	-0.56	-0.54
HADS (Anxiety)	-1.3	-1.1
HADS (Depression)	-0.4	-0.5
SDS	-0.6	-0.6
A negative value indicates an improvement in the score. None of the values between the two groups were statistically significant. HADS: Hospital Anxiety and Depression Scale; SDS: Sheeham Disability Scale		

process for pharmaceutical or dietary supplement options.

This is the optimistic view of these study results. On the more hesitant side is the fact that there was no placebo group. Each group could have simply improved because they each received, and knew they were receiving, something. A true clinical improvement that could be ascribed to a given intervention can only be shown in comparison to a placebo group, which we do not have in this case. Sometimes, new treatments are compared to known, standard-of-care treatments — in a study such as this one — in what are known as "noninferiority studies," but pentoxifylline does not fall into the category of an effective tinnitus treatment. As a medicine that may act to promote blood flow, it seemingly would be useful only for people suffering from vascular-type tinnitus, but there are many types of tinnitus; this distinction was not detailed in the study. Furthermore, in the introduction of the paper where pentoxifylline is mentioned, the reference[2] does not discuss pentoxifylline as a treatment option. Again, a placebo group would be needed, not a noninferiority study to a marginal treatment option.

With respect to clinical applicability, the 100% Caucasian demographic clearly limits extrapolation of these results to most clinicians' patient panels. And, the use of more validated, clinical metrics for depression and anxiety, such as the PHQ-9 and GAD-7, respectively, could have illustrated changes to which practicing clinicians could better compare their current therapies.

The *G. biloba* extract used (EGB761) and dose (120 mg, twice daily) are well-accepted treatments for several health conditions, including tinnitus. So the researchers picked the correct formulation of this plant, and did so with no conflicts of interest nor funding concerns. It was an impressive effort to study this plant for a difficult-to-treat condition, and a few interesting findings resulted. Next, it will be important to follow up these results in a double-blind, placebo-controlled trial. Until those results arrive in the medical literature, given the few other options, clinicians could consider a ginkgo treatment course for suffers of chronic tinnitus who are free of contraindications (i.e., worrisome potential plant-pharmaceutical interactions). ■

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MAGNESIUM

The Health Effects of Magnesium: Part 1

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Dr. Pantuso reports no financial relationships relevant to this field of study.

Editor's Note: Magnesium, an important dietary ingredient and supplement, has both long-standing and emerging clinical evidence for efficacy in treating a variety of health conditions. To do this mineral justice, we are covering this extensive information in two parts. Part 1 will focus on basic science and physiology, general dietary recommendations, supplemental forms, laboratory testing, and dosing. Part 2 will review some of the clinical trials and research on the connection between low magnesium intake and diseases, such as diabetes, as well as the data on the use of supplemental magnesium for treatment of these diseases.
— David Kiefer, MD, Editor

An essential mineral required by the human body, magnesium is involved in a diverse range of physiological functions and is a cofactor in an estimated 600 enzymatic reactions.[1-3] These

Summary Points

- Magnesium is the fourth most common cation in the human body.
- Magnesium is considered to be a shortfall nutrient and is a public health concern.
- Magnesium deficiencies have been shown to increase chronic inflammatory responses in animal models and are associated with chronic diseases in humans.

enzymatic reactions include those involved with the synthesis of nucleic acids and proteins involved with deoxyribonucleic acid and ribonucleic acid, mitochondrial function, glycolysis, and the maintenance of ionic gradients between intracellular and extracellular compartments.[1-3] Because of the importance of magnesium in the body, its availability is closely regulated in the human body through a number of mechanisms.[1-6] The three main mechanisms include gastrointestinal (GI) absorption, renal excretion and reabsorption, and exchange between bone magnesium stores and magnesium throughout the rest of the body.[1-6] When there is decreased intake of magnesium, there is increased absorption of magnesium in the GI tract and decreased renal excretion in the urine, and magnesium is progressively liberated from bone reserves.[5,6] Adequate magnesium in the diet results in decreased absorption in the GI tract, increased magnesium excreted into urine, and a higher amount of magnesium stored in the bone.[5,6] As a result of the body's ability to maintain magnesium homeostasis, it has been difficult to establish clinically relevant tests that reflect the body's magnesium status.[7] However, decreased magnesium levels demonstrated through dietary intakes, serum magnesium concentrations, and urinary magnesium excretions have been associated with a number of chronic diseases, including cardiovascular disease, prediabetes, type 2 diabetes, and chronic kidney disease.[1-4,7-11]

Signs and symptoms describing magnesium deficiency in humans were first reported in 1969; since then, experts have suggested various dietary reference intakes.[1-3,12,13] Symptoms of elevated magnesium (hypermagnesemia) and low magnesium (hypomagnesemia) are varied because of the number of diverse reactions in which magnesium is involved.[1-7] Hypermagnesemia symptoms include nausea, vomiting, flushing, muscle weakness, slurred speech, tachycardia, and, on EKG, prolongation of PR, QRS, and/or QT complexes.[1-4] Hypomagnesemia symptoms depend on the severity of the deficiency and on any concurrent electrolyte disturbances, such as hypocalcemia and or hypokalemia.[1-4] A general symptom is fatigue, but more specific symptoms include neuromuscular symptoms, such as tremors, tetany, nystagmus, and arrhythmias.[1-4] A classic sign of severe hypomagnesemia is hypocalcemia.[1-4]

Clinical magnesium deficiency signs have not been recognized routinely in the healthy population. Individuals with chronic health issues, such as migraine, obesity, cardiovascular disease, and diabetes, have been found to have low magnesium intake and/or magnesium status.[1-4] The normal total serum magnesium concentration range is considered to be between 1.7 and 2.3 mg/dL.[1-4] Patients with serum magnesium levels < 1.7 mg/dL are considered to be hypomagnesemic, and patients with levels < 1.2 mg/dL are considered to have severe hypomagnesemia.[1-4] Patients with serum levels > 2.5 mg/dL are hypermagnesemic and this level is rarely seen in people with normal kidney function.[1-4] Because 99% of magnesium is intracellular, serum magnesium concentrations are not reflective of total body magnesium levels, and may not be the most accurate laboratory test for quantifying magnesium status.[1-4]

Recent population studies have demonstrated decreased magnesium intake. For example, the U.S. Department of Agriculture reports that the average magnesium intake is 228 mg/day for women and 323 mg/day for men, which is below the RDA.[14] In the National Health and Nutrition Examination Survey I (NHANES) 2007-2010 report, the authors found that the majority of teens and adults over the age of 70 years consumed less than their estimated average requirement (EAR) of magnesium per day.[15] These reports of decreased magnesium intake instigated the 2015 Dietary Guidelines Advisory Committee to consider magnesium a shortfall nutrient that is being under-consumed relative to the EAR for many Americans.[16]

RECOMMENDED DIETARY ALLOWANCE (RDA) AND ESTIMATED AVERAGE REQUIREMENT (EAR)

RDA for magnesium varies by age and sex. For females 19-30 years of age it is 310 mg/day and for males 19-30 years of age it is 400 mg/day.[12] (*See Table 1.*) Requirements for magnesium increase during pregnancy and lactation.[12] (*See Table 2.*)

Tolerable upper limits exist only for supplemental magnesium and are as follows: 350 mg for all adults, 110 mg for children between 4 and 8 years of age, and 65 mg for children between 1 and 3 years of age.[12]

Current RDAs are determined from the EAR that is set by official committees.[2,7,17] The EARs are defined as the daily intake required to meet 50% of the healthy population needs.[2,7] The RDA is the daily

Table 1: Recommended Dietary Allowance for Magnesium in Males and Females[12]		
Age	**Male**	**Female**
Birth to 6 months	30 mg	30 mg
7-12 months	75 mg	75 mg
1-3 years	80 mg	80 mg
4-8 years	130 mg	130 mg
9-13 years	240 mg	240 mg
14-18 years	410 mg	360 mg
19-30 years	400 mg	310 mg
31-51+ years	420 mg	320 mg

intake that is required to meet 98% of the healthy population's daily requirement.[2,7] Since researchers investigating the EARs and RDAs of magnesium have not been able to adequately determine total body magnesium status and associate that value with magnesium intake, the current RDAs are thought to be inadequate.[2,7,17] Additionally, the current RDAs and EARs have been called into question since the U.S. food supply has changed and the incidence of diseases, such as diabetes and obesity, affect magnesium status.[2,4,7,17]

MAGNESIUM PHYSIOLOGY

Magnesium is absorbed throughout the GI tract, with the ileum and jejunum absorbing an estimated 78% of dietary magnesium.[1-4] Two transport mechanisms are responsible for the absorption of magnesium.[1,2,5] One transport mechanism is passive and the other is active.[1,2,5] The passive diffusion of magnesium occurs in the small intestine and is responsible for 80-90% of magnesium absorption. The active transport mechanism is the prevailing mechanism when intestinal magnesium concentrations are low, and it relies on the transient receptor potential channel melastatin proteins (TRPM6 and TRPM7).[1,2,5] The active transport system is responsible for 10-20% of total magnesium absorbed in the distal small intestine and colon.[5] However, when magnesium levels are low, the active transport system can increase absorption to 30-50% of ingested magnesium.[1,2,5,18] Once magnesium is absorbed into the bloodstream it is distributed throughout the body. Blood magnesium is found in the serum (0.3% of total body magnesium) and red blood cells (0.5% of total body magnesium). The bone is the most significant storage area for magnesium; an estimated 53% of total body magnesium is in the bone. The homeostasis of magnesium is largely managed by the kidney, GI tract, and bone. Magnesium excretion is controlled mostly by the kidney, which can filter up to 2,400 mg of magnesium per day, with approximately 5% excreted in the urine and 95% reabsorbed. The majority of the reabsorption of magnesium takes place in the loop of Henle and not in the proximal tubule.The plasma concentration of magnesium is the main factor in the reabsorption of magnesium by the kidney. However, reabsorption also is affected by hormones (parathyroid hormone, calcitonin, glucagon, and estrogen) and certain medications.[1,2,5,18] (*See Table 3.*) For example, diuretics and certain chemotherapy medications can cause abnormally high magnesium excretion.[19-21] Use of proton pump inhibitors (PPIs) for a year or more are associated with hypomagnesemia.[20,21] The PPIs may decrease the active absorption of magnesium through the TRPM protein channels.[20,21]

When medications are coupled with diseases that either reduce absorption through the gut or increase excretion through the kidney, hypomagnesemia can result.[1,2,20,21] There also are heritable contributions to serum magnesium that negatively affect magnesium status including TRPM6 mutations, which decrease the absorption of magnesium and result in renal magnesium wasting.[1]

THE EFFECT OF MAGNESIUM ON ANIMAL PHYSIOLOGY

Magnesium deficiency has been found to induce inflammatory responses and acute phase proteins in animal and in-vitro studies.[2,4,8] It was first reported in 1932 that magnesium deprivation in rats resulted in an increased inflammatory response.[22] Research continued on magnesium and its effects on the immune response, and in 2007, it was reported that limiting magnesium to 10% or less than the animals' daily requirement affected an increased inflammatory response.[23] These animal studies had short durations and the results are not likely translational.[2,8] However, the authors of smaller animal studies have demonstrated that a long-term magnesium deficiency that is 25-50% of the requirement also resulted in increased inflammatory responses.[2,8] The effects of a marginal magnesium deficiency are further affected by deficiencies in other anti-inflammatory compounds, such as omega-3 fatty acids, vitamin E, and selenium.[2,8] The plausible mechanism of action of how magnesium deficiency increases inflammation is through increased priming of phagocytic immune cells.[2,8] The increased intracellular calcium results from magnesium deficiency interfering with calcium transport, which may result in increased priming of the phagocytic immune cells.[2,8] Increased priming in the phagocytic immune

Table 2: Recommended Dietary Allowance for Magnesium in Females During Pregnancy and Lactation[12]

Age	Pregnancy	Lactation
14-18 years	400 mg	360 mg
19-30 years	350 mg	310 mg
31-51+ years	360 mg	320 mg

cells results in increased production and release of pro-inflammatory cytokines, such as substance P and tumor necrosis factor-alpha. The priming of the phagocytic cells also increases the activation of the transcription factor nuclear factor-kappa B, which results in the expression of numerous inflammation-related genes.[2,8] Chronic activation of the phagocytic cells increases the generation of reactive oxygen species, which leads to inflammatory stress that is related to the development of chronic diseases.[2,4,8]

MEASURING MAGNESIUM STATUS

Serum magnesium. Total serum magnesium is the test most frequently ordered to assess magnesium status, but investigators have found it to be unreliable in recent literature reviews.[9] In addition to not accurately reflecting total body magnesium status, the reference ranges for the total serum magnesium test were established from data taken from a U.S. study conducted during 1971 through 1974 in 15,820 participants who were between 18 and 74 years of age and who were presumed healthy. The normal reference range for the total serum magnesium test was established by taking the central 95th percentile, resulting in the normal reference range of 1.7-2.3 mg/dL.[9,24] This reference range is problematic and may not be relevant as Americans in the 21st century have been found to consume less dietary magnesium.[9,15] Investigators have found recently that individuals with chronic disease risk factors, such as inflammation, glucose intolerance, and elevated blood pressure, had a subclinical or chronic latent magnesium deficiency, with total magnesium serum levels between 1.7 and 2.0 mg/dL.[4,9]

Red blood cell magnesium testing. Erythrocytes contain elevated concentrations of magnesium compared to the serum.[2,9,18,25] Erythrocyte magnesium levels vary depending on the age of the erythrocyte.[9] However, the bulk of the studies using red blood cell (RBC) magnesium endpoints are not considered to be sufficiently robust or reliable.[9] Also, the studies measuring RBC magnesium did not use a method that is validated through intercompartmental sampling.[9] Because of the lack of studies demonstrating that RBC magnesium testing is reliable and an adequate representation of the body's magnesium pool, it is not a recommended standalone test to evaluate magnesium levels in the body.[9]

Urinary magnesium. Because magnesium is excreted by the kidneys into the urine, and excretion changes depending on whether an individual is deficient or sufficient, urine magnesium testing may be valuable in evaluating magnesium status.[9] No standard has been set for urinary magnesium excretion that indicates a deficiency.[9] Controlled experiments that measure 24-hour urinary magnesium excretion have found that 40-80 mg is the range that is excreted when magnesium intake is < 250 mg/day, and 80-160 mg is the daily range excreted when intakes are > 250 mg/day. These amounts are independent of gender. Urinary magnesium excretion changes within a few days when the magnesium intake changes to > or < 250 mg/day.[9]

Ruling out hypomagnesemia in patients who are symptomatic with a total serum magnesium level is important. For patients who may be at risk for a subclinical or chronic latent deficiency and/or suffer from a chronic disease, ordering a total serum magnesium level is warranted.[1,2,4,9] Combining the total serum magnesium level with a urinary magnesium excretion (available at most major labs) along with a dietary magnesium history appears to be the best method for getting a valid assessment of magnesium status.[1,9,21] Magnesium deficiency should be considered as a potential contributing factor to chronic diseases when a total serum magnesium level is < 2.0 mg/dL, urinary magnesium excretion is < 80.0 mg/day, and magnesium intake is < 250 mg/day.[4,9]

FOOD SOURCES

Food sources rich in magnesium include whole seeds, unmilled grains, leafy green vegetables, legumes, and nuts.[5] For example, almonds contain 80 mg of magnesium per 1 ounce serving and cooked black beans contain 60 mg per half cup.[12] It is theorized that one major contributor to decreased magnesium consumption is lower amounts of magnesium in the food supply.[4,17] The mineral content of the soil correlates directly to the concentration of minerals in the plants growing in that soil. Studies investigating the changes in concentrations of minerals in produce from the 1940s to the end of the 20th century indicate median declines of between 5% and 40% in fruits and vegetables.[17] The magnesium content of cheese and meat also has declined, most likely due to decreased magnesium in animal feed. The exact measurement of magnesium content in foods is difficult to define since many variables, including processing, pretreatment of foods, and different methods of analysis, affect magnesium concentration in foods.[17]

Table 3: Effects of Medications on Magnesium Status and Recommendations for Clinical Dosing		
Medication Class	**Effect on Magnesium Status**	**Clinical Recommendation**
Bisphosphonates	High levels of magnesium can decrease the absorption of oral bisphosphonates used to treat osteoporosis.	Separate administration of magnesium and bisphosphonate by two hours.
Some antibiotics	Formation of insoluble complexes occurs with tetracyclines as well as quinolones.	Take antibiotics two hours before or four to six hours after magnesium-containing supplements.
Diuretics	Loop diuretics increase the urinary excretion of magnesium, which can lead to magnesium depletion. Potassium-sparing diuretics reduce magnesium excretions.	Consider alternative medication classes.
Proton pump inhibitors (PPI)	Can cause hypomagnesemia when taken for prolonged periods, such as more than one year.	Magnesium oral supplementation normally will increase the magnesium levels; however, in a quarter of cases, supplements did not raise the serum magnesium level after the PPI was discontinued. FDA advises healthcare professionals to consider measuring patients' serum magnesium levels prior to initiating long-term PPI treatment and to periodically check magnesium levels in these patients.

DIFFERENT SUPPLEMENTATION FORMS

Oral supplementation. Magnesium absorption efficiency is affected by other dietary factors and, when given as a supplement, its chemical form. Lactose, fructose, and glucose enhance magnesium absorption, while other dietary factors, including fiber, high levels of zinc, oxalate, and free fatty acids, are known to inhibit magnesium absorption. Absorption of magnesium ranges from 35% to 70% in human studies investigating low-to-high magnesium intake. Normal intakes demonstrate that 30-40% of dietary magnesium is absorbed.[5] However, in patients with decreased absorption due to inflammatory bowel disease, other inflammatory conditions affecting the small intestine, or surgical modifications, magnesium deficiency may be more common. A number of different forms of magnesium are sold in supplement form. Some evidence suggests that magnesium supplements that dissolve in liquid are better absorbed, and that magnesium in the forms of citrate, chloride, lactate, and aspartate are more bioavailable than magnesium in its oxide or sulfate forms.[12] These studies need to be taken with a grain of salt since they are small and it is difficult to assess magnesium status, as noted earlier.

Labdoor, a third-party company that analyzes supplements for quality and label claims, analyzed 34 oral magnesium supplements on the market for elemental magnesium levels and contamination of heavy metals.[26] Of the 34 supplements, the magnesium per serving ranged from 38.1 to 691.2 mg, with an average of 331 mg per serving.[26] The supplemental magnesium amounts deviated from the label claims by an average of 11.5%. Of the products reviewed, 19 exceeded the tolerable upper intake level of magnesium, while 15 met the daily RDA.[26] The products deviated from their label claims in the amount of magnesium in the supplement, with one supplement only containing 9.5% of the label claim and another having 97.5% more than the label claim.[26] In 25 of the 34 supplements, the level of arsenic per serving was projected to exceed California Proposition 65's proposed safe daily intake limit for inorganic arsenic.[26] Six products contained the adulterant titanium dioxide, used as a whitening agent.[26] Magnesium is sourced from sea water and mining, which makes heavy metal testing an important consideration when recommending magnesium supplements. Another independent supplement testing company, ConsumerLab, tested 27 oral magnesium supplements and determined that four were inadequate.[27] It was found that one product did not reflect the amount on the label, two products failed the capsule/tablet disintegration test, and one product made health claims not consistent with FDA regulations.[27]

Skin absorption. There is limited, contradictory evidence regarding the transdermal absorption of magnesium.[28] Much more research needs to be performed to understand whether clinically significant amounts of magnesium are absorbed through the skin.[28,29]

Intravenous. Intravenous (IV) magnesium is used to treat a number of conditions. Major medical organizations worldwide recommend magnesium sulfate for

the prevention of eclampsia in women with pre-eclampsia.[30] Magnesium sulfate also is a first-line therapy for long QT-related ventricular ectopic beats or torsades de pointes.[11,21] Benefits are noted in patients who have normal serum magnesium levels at baseline. Magnesium sulfate also is recommended in multifocal atrial tachycardia in IV form if serum magnesium measures < 1.4 mg/dL.[11,21] Integrative care providers that perform nutrient IV therapies commonly use magnesium, which is also a component of the Myers' cocktail previously reviewed in this publication (See *Integrative Medicine Alert*, April 2017).[31]

SUMMARY

Magnesium is one of the least studied macrominerals, especially when compared to iron and calcium. Research has been hampered by less than ideal diagnostic tests and the difficulty of making a clinical diagnosis using the nonspecific clinical signs and symptoms. Also, the presence of common comorbidities, such as diabetes and cardiovascular disease, further complicates the suspicion and diagnosis of magnesium deficiency. Currently, there is concern that the U.S. population may not be consuming enough magnesium through dietary intake. About 48% of Americans are not consuming enough magnesium, which may increase their risk of chronic disease and mortality, a fact that is further complicated by comorbidities and certain medication use.[2,4]

Magnesium deficiency may be an important factor in patients' health. At this time, it is difficult to assess the parameters for a subclinical magnesium deficiency in patients. Better testing is needed to assess magnesium deficiency, particularly in its mild to moderate forms. Much more research needs to be performed so that we know the ideal daily magnesium intake for various demographics and can develop better testing to detect deficiencies in our patients.

Part two of this magnesium review will appear in an upcoming issue and address human clinical trials and clinical recommendations. ■

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CME QUESTIONS

1. **Which statement regarding Parkinson's disease (PD) treatment and management is false?**
   a. Historically the motor symptoms of PD have been the focus of treatment, although there is growing awareness of nonmotor symptoms and the implication for disability from these symptoms.
   b. Motor symptoms of PD are best treated with medication and/or surgery; the role of exercise is not well-established for these symptoms and needs substantial further investigation.
   c. Conventional treatment of PD includes medication and/or surgery as well as stretching and resistance training or other forms of physical exercise.
   d. The Kwok et al study showed that a specific form of mindfulness-based yoga was as effective as a conventional exercise program in addressing motor symptoms of PD, and more effective in addressing some of the psychological symptoms of this disorder.

2. **Which of the following is true regarding the study on ginkgo and tinnitus?**
   a. The ginkgo treatment group used ginkgo tea twice daily.
   b. The ginkgo treatment group showed improvement in tinnitus scores similar to the group treated with pentoxifylline.
   c. The pentoxifylline group showed more improvement in depression and anxiety scores.
   d. There were more adverse effects in the ginkgo group.

3. **Which of the following is true about magnesium?**
   a. There is no renal excretion or absorption.
   b. The majority of magnesium is absorbed in the small intestine.
   c. Absorption of magnesium after oral intake approximates 100%.
   d. Serum magnesium testing accurately approximates total body magnesium levels.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

The Health Effects of Magnesium: Part 2

Light Therapy for Depression in Parkinson's Disease

Nuts vs. Carbs in Patients With Diabetes

Dosing for Greatest Iron Absorption