

Integrative Medicine

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the latest developments in integrative therapies [ALERT]

DIABETES

ABSTRACT & COMMENTARY

Integrative Therapies for Type 2 Diabetes Mellitus: Micronutrient Supplements

By *William C. Haas III, MD, MBA*

Integrative Medicine Fellow, Department of Family and Community Medicine, University of Arizona, Tucson

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

Type 2 diabetes mellitus (T2DM), characterized by peripheral insulin resistance and pancreatic β -cell dysfunction, represents a worldwide public health concern, as more than 400 million people are expected to be affected by the year 2030.¹ Despite advances in the treatment for T2DM (long-acting insulins, GLP-1 agonists, DPP-4 inhibitors, etc.), achieving optimal glycemic control remains a challenge, partly as a result of non-adherence to complex medication regimens. Now more than ever, uncovering new insights for the prevention and management of T2DM is essential for improving outcomes and providing patient-centered care.

Regardless of whether medical providers are aware, diabetic patients frequently experiment with integrative modalities. In fact, according to one study, patients with

T2DM are 1.6 times more likely to try complementary and alternative therapies as compared to non-diabetics.² Moreover, among the various modalities reported, botanical remedies and micronutrient supplements consistently rank at the top of several surveys.^{3,4}

Part one of this two-part review will focus on the role of micronutrients in the prevention and management of T2DM. Micronutrients, including vitamins and minerals, are required for many functions in the body, including glucose metabolism, insulin activity, and prevention of tissue oxidation.⁵ Unfortunately, chronic hyperglycemia has been shown to reduce the levels of various micronutrients in the body,⁶ which further disturbs glucose regulation and potentially worsens diabetic complications.⁷ Over the past few decades, researchers have examined the effects of supplementing

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Summary Points

- Type 2 diabetes is associated with a number of micronutrient deficiencies.
- Zinc is supported with the best evidence for improving glycemic control among type 2 diabetics.
- Recommendations for micronutrient supplementation among diabetics is largely limited by a paucity of high-quality studies.

these micronutrient deficiencies, and some of the most commonly encountered supplements in clinical practice are reviewed below.

ALPHA-LIPOIC ACID

A potent lipophilic antioxidant, alpha-lipoic acid (ALA) is a naturally occurring compound found in trace amounts in organ meats and vegetables. Unlike the other supplements reviewed, ALA is used primarily for the treatment of painful diabetic neuropathy. Its mechanism for improving neuropathic pain may be related to an improvement of nerve blood flow as well as a reduction in oxidative stress.⁸

ALA has been extensively studied in both intravenous (IV) and oral forms. Initial investigations, including the original ALADIN (Alpha-Lipoic Acid in Diabetic Neuropathy) and SYDNEY (Symptomatic Diabetic Neuropathy Trial) trials, focused on treating diabetic neuropathy with IV ALA. Both studies found that 600 mg of IV ALA daily significantly improved symptom severity as compared with placebo when used for periods of 2-3 weeks.^{9,10} These studies prompted additional investigations focusing on the use of oral ALA. The SYDNEY 2 trial compared three different doses of oral ALA (600 mg, 1200 mg, and 1800 mg daily) against placebo. After 5 weeks, all three doses outperformed placebo with near equal improvements in total symptom scores across the different doses.¹¹ Unlike the SYDNEY 2 trial, the ALADIN 3 trial did not find a statistically significant difference between placebo and 1800 mg of oral ALA daily, although the results trended toward improvement.¹² Recently, results of a 4-year, multicenter, randomized, double-blind trial of 600 mg of oral ALA daily found clinically meaningful improvements in neuropathy and a prevention in the progression of neuropathic impairments.¹³

Overall, studies support both IV and oral ALA for the treatment of diabetic neuropathy. Oral ALA is clearly the easiest and most accessible form for patients to use, with 600 mg per day being the ideal dose when balancing cost and potential side effects. At doses > 1200 mg daily, patients have been noted to experience nausea, vomiting, and/or vertigo. The most commonly reported adverse events include heart rate and rhythm abnormalities.¹³ The cost for a 1-month supply at 600 mg daily ranges between \$25-40. Of note, the R isomer of ALA may be more effectively utilized in the body compared to other formulations and should be considered when making recommendations to patients. Additionally, patients should be advised not to confuse this supplement with alpha-linolenic acid, which is also abbreviated as ALA.

CHROMIUM

Originally discovered in brewer's yeast, chromium is a trace element commonly found in its trivalent form. It is believed to be necessary for both glucose and lipid metabolism.^{14,15} Severe chromium deficiency has been reported to cause reversible insulin resistance and diabetes.¹⁶ Through its action with glucose tolerance factor, chromium increases insulin receptors, improves insulin binding, and enhances beta cell sensitivity.¹⁷

Chromium is a widely marketed and commonly purchased supplement for improving glycemic control,¹⁸ yet the evidence is split at best. One of the initial studies on chromium yielded an impressive 1.0% hemoglobin A1c lowering effect after supplementing diabetics with 200 mg of chromium picolinate daily for 4 months.¹⁹ Ten years later, a meta-analysis, which included 14 randomized, controlled trials, reported that chromium significantly improved hemoglobin A1c levels (-0.6%;

95% confidence interval [CI], -0.9% to -0.2%) among type 2 diabetics.²⁰ Unfortunately, a closer look of this meta-analysis revealed that the positive effect was driven primarily by the aforementioned study, which has been criticized for its poor methodological quality, including inadequate blinding as well as concerns for detection and selection bias.²¹ Further clouding the picture, other more recent meta-analyses reached different conclusions regarding chromium's positive effect on glycemic control.^{22,23}

Despite the mixed evidence for chromium in the management of T2DM, the majority of researchers agree that the existing evidence is low in quality. The conservative recommendation would be to dissuade diabetic patients from spending money on this supplement at this time. Patients who insist on using chromium should be advised to avoid doses > 1200 mcg/day, given reports of renal failure.^{24,25} Other more common side effects include abdominal discomfort and bloating.

MAGNESIUM

Despite being the fourth most abundant mineral in the body, magnesium is frequently consumed in inadequate amounts.²⁶ Unfortunately, inadequate dietary intake of magnesium has been linked to various disease states, including diabetes mellitus.²⁷ Research further suggests that hypomagnesemia among diabetics may contribute to worse glycemic control as well as an increase in retinopathy, nephropathy, and foot ulcers when compared to those with normal magnesium levels.²⁸

With regards to supplementation, evidence suggests that higher intakes of magnesium may decrease the risk of T2DM, but improvements in glycemic control are not validated. In a 15-year prospective cohort study involving nearly 2000 patients, increased magnesium intake was noted to be a significant protective factor against the development of T2DM.²⁹ These findings were further supported by another meta-analysis of 13 prospective studies, and the association was not modified by geographic region, follow-up length, or gender.³⁰ Shifting focus to glycemic control, a meta-analysis of nine randomized, double-blind, controlled trials found that although magnesium supplementation potentially lowered fasting glucose levels, no significant decrease in hemoglobin A1c levels were seen.³¹ Another meta-analysis of seven cohort studies concluded that magnesium supplementation for the reduction of glucose levels is inconsistent.³²

Ultimately, adequate magnesium intake is likely a protective factor against the development of T2DM; however, current evidence does not support supplementation for the treatment of diabetes. The most prudent recommendation for patients with limited

resources would be to skip magnesium supplements all together and consume a variety of magnesium-containing foods (leafy green vegetables, nuts, fish, chocolate) given their overall health benefits. For patients desiring to supplement beyond food sources, dosing typically starts at 100 mg daily, working up toward 300-600 mg daily, keeping in mind that higher doses may cause diarrhea.

VITAMIN D

Best known for its role in calcium metabolism and bone growth, vitamin D is a fat-soluble vitamin that acts as a hormone at various sites in the body.³³ In fact, several studies over the past decade have reported associations between vitamin D deficiency and many extra-skeletal diseases, including T2DM.^{34,35} With regard to glucose homeostasis, vitamin D is believed to regulate insulin receptor expression as well as stimulate insulin release from pancreatic B-cells.^{36,37}

Despite the striking prevalence of vitamin D deficiency among type 2 diabetics, evidence does not support supplementation at this time.³⁸ Several randomized, controlled trials and meta-analyses have shown that neither short-term nor long-term vitamin D supplementation improves glycemic control.^{39,40,41,42} Unfortunately, this lack of efficacy leaves clinicians stuck when facing evidence that vitamin D deficiency increases both all-cause and cardiovascular mortality among type 2 diabetics.⁴³ Fortunately, one meta-analysis has found that taking 500 IU of vitamin D per day decreased the risk of developing diabetes by 13% when compared to intake below 200 IU/day.⁴⁴

Recommendations for vitamin D supplementation among type 2 diabetics could eventually change as several variables remain unknown (optimal dosing, duration of therapy, etc). However, until clarity develops, diabetics should not routinely supplement with vitamin D for the expressed purpose of improving glycemic control. For those patients with other indications, supplementation should include 800-1000 IU daily, and target a serum 25-hydroxyvitamin D level between 30-50 ng/mL. Keep in mind that although vitamin D is largely considered safe, prolonged high-dose supplementation (50,000 IU/day), in rare circumstances, can lead to hypercalcemia.

ZINC

An essential mineral in the human body, zinc is responsible for numerous enzymatic and cellular processes in addition to functioning as an antioxidant and anti-inflammatory agent.^{45,46,47} With regards to glucose metabolism, research has demonstrated that zinc plays an important role in the synthesis, storage, and release of insulin.^{48,49,50} Zinc deficiency is relatively common among diabetic patients, and evidence supports both a cause and effect association — deficiency increases diabetes risk and diabetes impairs zinc metabolism.^{51,52,53}

The research on zinc supplementation among diabetics has focused primarily on glucose control, with an isolated study evaluating diabetic peripheral neuropathy. With regard to glucose control, two separate meta-analyses found that zinc supplementation decreased hemoglobin A1c by approximately 0.6%.^{54,55} Although several of the studies analyzed included zinc in combination with other vitamins and minerals, a secondary analysis of zinc therapy alone demonstrated similar beneficial effects on glycemic control.⁵⁵ Naturally, the question of prevention arose, given the reported zinc deficiency among many diabetics; however, a Cochrane review in 2015 concluded that the current evidence does not support zinc supplementation for the prevention of T2DM.⁵⁶ Finally, when looking at diabetic complications, specifically peripheral neuropathy, supplementation with 660 mg of zinc sulfate daily for 6 weeks improved motor nerve conduction velocities compared to placebo in a small, randomized, double-blind trial.⁵⁷ Unfortunately, follow-up studies on zinc for diabetic neuropathy have been limited.

Ultimately, zinc may be a reasonable supplement to consider for improving glycemic control in type 2 diabetics, keeping in mind that this recommendation is largely based on two meta-analyses with a great deal of heterogeneity. The dose and formulation most commonly tested for glycemic control was 30 mg of zinc sulfate per day. Zinc is generally well-tolerated, aside from reports of nausea, vomiting, and metallic taste. Of note, several cases of copper deficiency have been associated with high-dose zinc supplementation.⁵⁸

CONCLUSIONS

Mounting evidence confirms that type 2 diabetics are deficient in several vitamins and minerals; however, the manner in which these deficiencies influence the progression of type 2 diabetes is not always clear. Given the growing interest of micronutrient supplements among patients with T2DM, researchers have expanded their study in the field. The current evidence most strongly supports the use of zinc for improving glycemic control with positive but mixed evidence for chromium. Magnesium may be best suited for preventing T2DM, but as with vitamin D, it probably does not play a role in the active management of diabetes. With this said, there is always a role for finding these nutrients, when possible, in food sources as part of an overall healthy diet. Finally, ALA offers promise to patients suffering from peripheral neuropathy. Despite these general conclusions, clinicians should bear in mind that the overall quality of existing evidence remains limited due to a significant amount of heterogeneity among the patient populations and supplements studied. As diabetic patients continue to seek out additional treatment options, it will remain important to monitor the evolving research. ■

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ALZHEIMER'S DISEASE

ABSTRACT & COMMENTARY

Acupuncture and Alzheimer's Disease: A Review of a Meta-Analysis

By *Melissa Quick, DO*

Integrative Medicine Fellow, Mount Sinai Beth Israel Medical Center, New York City

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

SYNOPSIS: According to Zhou's recent research, acupuncture is a safe option that may be effective at improving cognitive function in patients with Alzheimer's disease when used in conjunction with certain pharmaceutical treatments.

SOURCE: Zhou J, et al. The effectiveness and safety of acupuncture for patients with Alzheimer disease: A systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2015;94:e933. doi: 10.1097/MD.0000000000000933.

To evaluate the effectiveness and safety of acupuncture in Alzheimer's disease (AD), two authors independently searched databases and extracted

data for this meta-analysis. The inclusion criteria were randomized, controlled trials (RCTs) with participants diagnosed with AD by common diagnostic criteria,

including the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders. Studies using acupuncture were included unless the trials compared different types of acupuncture or acupoints.

The initial search yielded 1703 results. After removing duplicates and eliminating review articles, animal experiments, papers focusing on the mechanism of AD, and unrelated topics, 10 RCTs were ultimately selected. From these trials, 585 participants were included in the meta-analysis. The included studies had sample sizes ranging from 16 to 49 participants, participants ages 46 to 81 years, and trial durations of 4 to 24 weeks. The specific acupuncture points used most frequently were noted, with the most common two (GV20 and ST36) used 40% among the 10 studies. Although each RCT utilized randomization, the details were unclear in half of the trials, even after the authors of the original trials were contacted. None of the RCTs blinded acupuncturists or participants, and there was no mention whether any of the studies used sham acupuncture.

Zhou accounted for the risk of bias in each study using the Cochrane Handbook for Systematic Reviews of Interventions. The 10 RCTs were evaluated in three groups based on comparisons: Group 1: “acupuncture versus drugs;” Group 2: “acupuncture plus donepezil versus the same donepezil alone;” and Group 3: “acupuncture versus no treatment.” Multiple different neurocognitive scales were used to evaluate treatment endpoints. These scales included the Mini Mental State Examination (MMSE) Scale, Hasegawa’s Dementia Scale, Alzheimer’s Disease Assessment Scale-Cognition (ADAS-cog), Activities of Daily Living (ADL) Scale, Functional Activities Questionnaire (FAQ), and the Montreal Cognitive Assessment (MoCA). All of the 10 trials used the MMSE and seven used the ADL scale for outcome assessments. For simplicity in this review, we will only mention Zhou’s analysis of these two scales in the above three groups.

In Group 1, the RCTs included a variety of “drugs:” donepezil, almitrine and raubasine, dihydroergotoxine, nimodipine, and piracetam. For the MMSE outcome of Group 1, Zhou found a large amount of heterogeneity ($P = 57\%$) but noted that this may primarily be due to one particular study that was an unpublished master’s thesis with shorter duration than the other five studies. The mean differences (MD) of MMSE scores for the six RCTs was 1.05 (95% confidence interval [CI], 0.16-1.93; $P = 0.02$) using the random model and 0.54 (95% CI, 0.02-1.07; $P = 0.04$) using the fixed model, neither of which was significantly different. For the ADL outcome of Group 1, the MD was -2.80 (95% CI, -4.57 to -1.02; $P = 0.002$) using the fixed model.

Summary Points

- Management of the cognitive and behavioral symptoms of dementia is a growing concern, as the prevalence of Alzheimer’s disease is expected to increase in the coming years.
- Current conventional treatment consists primarily of pharmaceuticals with limited efficacy and a high risk of adverse effects.
- Acupuncture is a safe modality that may be offered alone or in conjunction with pharmaceutical treatment to possibly improve cognitive function in individuals with Alzheimer’s disease.

Table: Acupuncture Groups Based on Comparisons

Group 1	Group 2	Group 3
Acupuncture vs drugs	Acupuncture plus donepezil vs the same donepezil alone	Acupuncture vs no treatment

The results of Group 2 combined three RCTs and showed a MD of 2.37 (95% CI, 1.53-3.21; $P < 0.0001$) for the MSSE scale, indicating a statistically significant difference between the “acupuncture plus donepezil” and “donepezil alone” groups in improving the MMSE score.

Group 3 involved only one RCT evaluating the MMSE and ADL scores and, thus, was not a true meta-analysis. The MD of the MMSE outcome was statistically significant (3.74; 95% CI, 1.34-6.14; $P = 0.002$), but the MD of the ADL outcome was not (-8.82; 95% CI, -19.83 to 2.19; $P = 0.12$).

The safety of acupuncture was addressed separately, evaluating 141 studies consisting of 3416 AD patients treated either with acupuncture or acupuncture and another therapy. No studies reported severe adverse events. Adverse reactions related to acupuncture occurred in only seven cases. Of these seven, the reactions were described as tolerable and not severe.

■ COMMENTARY

AD is an irreversible, progressive form of dementia that causes memory loss and cognitive decline. AD is the most common form of dementia and is a complex disease characterized by an accumulation of β -amyloid (A β) plaques and neurofibrillary tangles composed of tau amyloid fibrils.¹ Today, of the 5.3 million Americans with AD, 5.1 million are ≥ 65 years of age and 81% are

≥ 75 years of age.² Two-thirds of patients with AD are women.³ The prevalence of AD increases annually across the globe. It is estimated that worldwide, the number of individuals suffering from dementia will increase to 75.6 million in 2030, and 135.5 million in 2050.⁴ Individuals with AD, along with their family, friends, and caregivers, are tremendously affected on personal, emotional, financial, and social levels. In 2010, the total estimated worldwide cost of dementia was \$604 billion.⁵

Given the incredible burden that AD puts on all of us — as family members, friends, and clinicians — the search for adequate symptom control and ultimately prevention is crucial. In particular, managing the behavioral aspects of AD, such as sleep disorders, anxiety, depression, and agitation, pose significant challenges for providers. Indeed, in 2010, a group called Alzheimer's Disease International urged governments to take a more prominent role in research and care for those affected by AD.⁵ In 2011, President Barack Obama signed into law the National Alzheimer's Project Act (NAPA) with the mission of funding research, provider education, and awareness of AD.⁶ Acupuncture, among other integrative approaches, offers promise to ameliorate some of the cognitive and behavioral symptoms associated with AD.

Zhou's meta-analysis exemplifies the type of research necessary to evaluate the utility of acupuncture. Acupuncture, the insertion and stimulation of needles at specific points on the body to facilitate recovery of health, is gaining popularity in the United States.⁷ Acupuncture is part of a larger system of healing within traditional Chinese medicine (TCM) and has been around for thousands of years. In addition to TCM acupuncturists, contemporary acupuncturists also include medical doctors who integrate physiologic aspects of the needling process along with traditional Chinese teachings.⁸

Understanding risk factors and the pathology of AD are paramount to prevention, early recognition, and monitoring and controlling symptoms. Briefly, the major risk factors² for AD include:

- Age older than 65 (though AD is *not* a normal part of aging)
- Genetics (a first-degree relative with AD along with inheriting one or two copies of the e4 form of apolipoprotein E [APOE] gene *may* increase the likelihood of developing AD)
- Mild cognitive impairment; cardiovascular disease (growing evidence links the health of the heart and blood vessels to brain health)
- Fewer years of formal education; decreased social and cognitive engagement
- Personal history of traumatic brain injury

The diagnosis of AD is largely clinical and historically has been made by a patient's primary care physician.

A physician generally makes a diagnosis by assessing a patient's complete medical and family history, gaining insight from family members, physical and neurologic examinations, and neurocognitive tests such as those listed above.

In 2011, the National Institute on Aging and the Alzheimer's Association suggested revised criteria and guidelines for diagnosing AD. These modified guidelines categorize AD into three categories (preclinical Alzheimer's, mild cognitive impairment due to Alzheimer's, and dementia due to AD), and also propose the use of biomarkers to both identify and treat those with the disease.⁹ It should be emphasized that these guidelines have not been validated but do show promise in our clinical approach to AD. The participants in Zhou's meta-analysis were likely in the latter two categories.

The 10 trials included in Zhou's study were primarily within the last decade, ranging from 2001-2014. Perhaps unsurprisingly, given that acupuncture originated in China, all 10 studies were in Chinese. Zhou notes that none of the reviewed RCTs contained information about the degree of hippocampal atrophy, as no study utilized magnetic resonance imaging (MRI). MRI, along with certain biomarkers such as the e4 form APOE gene, are gaining momentum as additional ways in which to both diagnose and monitor the progression of AD.² Future acupuncture studies would benefit from reviewing additional objective endpoints such as imaging and serum biomarkers.

In Zhou's review, neurocognitive tests were the *only* way in which interventions were monitored. Six different neurocognitive assessments were used and compared in the 10 studies above. This variety of outcome measurements leads to an unavoidable degree of heterogeneity in this meta-analysis, except when evaluating the MMSE, which was the only outcome used in all of the studies. The small sample sizes of studies utilizing other assessments, such as the MoCA, HDS, ADAS-cog, and FAQ, made meta-analysis impossible and thus effectiveness could not be sufficiently determined.

Interestingly, a recent study compared different cognitive and behavioral assessments in patients with AD and found similar correlations between test results.¹⁰ This indicates that the perceived heterogeneity between outcome measurements in this meta-analysis may be more homogenous than they initially appear to be. Furthermore, educational differences influence cognitive performance and may affect baseline and outcome scores.¹⁰ Future meta-analyses that utilize neurocognitive scales may benefit from including education levels as additional data points for interpretation.

Unfortunately, no pharmacologic or non-pharmacologic treatments available today slow or stop the neuronal damage or symptoms associated with AD.² Given the current suboptimal state of therapies for AD, many nonconventional modalities, such as mind-body therapies, botanicals, and dietary approaches, are being further explored as effective care options.¹¹ Indeed, a recently published National Health Statistics Report shows a linear increase in the use of acupuncture in general over the last decade.¹²

Interestingly, many of the medications used in the RCTs in Group 1 (acupuncture vs drugs) are not used in the United States to treat AD. For example, dihydroergotamine, nimodipine, piracetam, and almitrine and raubasine are not frequently used to treat AD in the United States. The FDA currently has approved five medications to treat AD symptoms: donepezil, galantamine, rivastigmine, memantine, and a combination pill including donepezil and memantine.¹³ Correspondingly, the applicability of the results of the meta-analysis of Group 1 to the U.S. population is limited.

Frustratingly, current medication regimens have limited efficacy and questionable short- and long-term clinical significance.¹⁴ Additionally, there have been significant adverse effects associated with commonly used pharmaceuticals for AD. Medications such as donepezil come with a long list of possible significant adverse reactions, the most significant of which include insomnia (2-14%) and gastrointestinal upset (nausea 3-19% and diarrhea 5-15%).¹⁵ In comparison, acupuncture is generally considered safe, with the most common risks consistent with those that could occur whenever penetrating the body with a sharp instrument, but quite rare in practice under a well-trained acupuncturist. A patient on anticoagulation should be vigilantly observed for deep bleeding, although there are no reported cases to date.⁸ Because acupuncture can sometimes be associated with an acute onset of euphoria, anxiety, or lightheadedness, all patients should be monitored during and after a treatment.

The analysis of Group 2, where a statistically significant difference was found in the improvement of the MD of MMSE scores between the “acupuncture plus donepezil” and the “donepezil alone” group, represents a truly admirable aspect of Zhou’s study. Group 2 analyzes studies using the FDA-approved drug donepezil. This medication is considered a current front-line treatment for AD in the United States; thus, these results offer more relevance to patients in this country. Group 2 *integrates* treatment modalities, rather than focusing on therapies individually. Indeed, Zhou points out that their systematic review is the only such review to evaluate the idea that acupuncture (an “alternative” modality)

being used *in conjunction with* pharmaceuticals (a more “conventional” treatment) may enhance the effect of pharmaceuticals.

Another novel aspect of Zhou’s study is that it is the first systematic review of acupuncture treatment for AD patients assessing safety. As discussed above, side effects were minimal in the meta-analysis. In general, acupuncture is considered safe in a geriatric population (those most likely to have AD), with the most common risks consistent with those that could occur whenever penetrating the body with a sharp instrument. A patient on anticoagulation should be vigilantly observed for deep bleeding, although there are no reported cases to date.⁸ Because acupuncture can sometimes be associated with an acute onset of euphoria, anxiety, or lightheadedness, all patients should be monitored during and after a treatment.

One aspect not addressed in Zhou’s study is the feasibility of actually performing acupuncture in challenging populations. Patients with dementia represent a unique challenge to acupuncture, as patients must cooperate with their acupuncturist (i.e., lying calmly and still) during a treatment. Interestingly, this study and the research reviewed does not address this aspect of treatment, perhaps because their participants were all in an earlier stage of AD and thus more capable of controlling their behavior. Further information on the practical approach to performing acupuncture on a patient with an altered sensorium would be beneficial for acupuncturists interested in helping this population.

Despite the positive intentions of this meta-analysis, several concerns within the study question its validity. Zhou acknowledges that selection and publication bias may decrease the quality of his evidence. All studies analyzed in this review were from China, thereby potentially limiting the applicability to other countries and other more heterogeneous populations. Also the paucity of information on randomization and allocation aspects of the 10 RCTs examined raise concerns of the methodology used in the original studies.

Although any acupuncture trial has difficulty adequately blinding providers and recipients of acupuncture, this aspect was also not addressed in Zhou’s 10 RCTs and may impact the results. Conversely, it could be argued that participants with dementia may not recall that they had acupuncture, and therefore the concern of inadequate blinding on the patient’s part may be somewhat reduced in this unique population. A final consideration for the limitations of Zhou’s review is that none of the RCTs assess short- or long-term follow-up of their participants. Arguably one of the most important aspects of research for modalities to help patients with AD is to search for long-term amelioration of symptoms.

Future studies with long-term follow up of patients with any intervention will be the most useful.

Meta-analyses such as Zhou's are paramount to evaluating the safety and effectiveness of interventions of integrative treatments for AD. Though biases, small sample sizes, and heterogeneity of studies may have detracted from the significant outcomes in this study, acupuncture remains a promising adjunct treatment for patients with AD. Compared to the adverse effects of pharmaceuticals, the risks associated with acupuncture seem to be insignificant. Given the limited effectiveness of current conventional treatment approaches to AD, acupuncture seems to be a safe modality that may be offered alone or in conjunction with pharmaceutical treatment to possibly improve cognitive function and ADLs in individuals with AD. ■

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METABOLIC SYNDROME

ABSTRACT & COMMENTARY

Preventing Adolescent Metabolic Syndrome: A Lesson from Finland

By Donald J. Brown, ND

Managing Director, Natural Product Research Consultants, Seattle

Dr. Brown reports he is a retained consultant for Nature's Way.

SYNOPSIS: Adolescent metabolic syndrome predicts type 2 diabetes mellitus and subclinical atherosclerosis in adulthood. This Finish study found that repeated infancy-onset dietary intervention primarily aimed at reducing intake of saturated fat from infancy to early adulthood was effective in preventing adolescent metabolic syndrome.

SOURCE: Nupponen M, et al. Metabolic syndrome from adolescences to early adulthood. Effect of infancy-onset dietary counseling of low saturated fat: The Special Turku Coronary Risk Factor Intervention Project (STRIP). *Circulation* 2015;131:605-613.

The Special Turku Coronary Risk Factor Intervention Project (STRIP) was designed to study the effect of dietary intervention that begins in infancy and continues until the age of 20 years. The focus is on atherosclerosis risk factors. A prospective, randomized, controlled trial, the STRIP study recruited families with 5-month-old infants at well baby clinics in Turku, Finland, between February 1990 and June 1992. At the age of 6 months, 1062 infants were randomly allocated to an intervention (n = 540) or a control group (n = 522). The intervention

group received individual dietary counseling at least biannually until the age of 20 years. Parents received counseling for their child until age 7 years and, from then on, it was given directly to the child. The primary focus of the counseling was the replacement of saturated fat with unsaturated fat. Dietary counseling also included reduction of salt intake and the increased use of whole grains, fruits, and vegetables. A fixed diet was never ordered and the counseling was individualized with recent food records used to tailor dietary suggestions. The

Summary Points

- Adolescent metabolic syndrome (MetS) increases the risk of type 2 diabetes and subclinical atherosclerosis in adulthood.
- The results of this study indicate that repeated dietary counseling beginning in infancy and extending to early adulthood significantly decreases the risk of adolescent MetS.

primary prevention of smoking was introduced at the age of 8 years and a physically active lifestyle was encouraged but not structured for the children. Children in the control group were seen at similar intervals and received only basic health education but not dietary counseling.

The study report is based only on those participants who were tested for metabolic syndrome (MetS) within a study visit between 15 and 20 years of age. Included in the definition of MetS were waist circumference, blood pressure, triglycerides, glucose, and HDL-C. Because there is no universally accepted definition of adolescent MetS, several criteria were applied including the modified International Diabetes Federation definition of MetS (80th/20th percentile cutoff points for each component) as well as the National Cholesterol Education Program definition and others. A total of 534 participants were included in the analysis at age 15 years. There were 127 participants lost to follow-up between ages 15 and 20 years, and this was higher in the intervention group compared to the control group (29% vs 19%; $P = 0.008$).

At 15 to 20 years of age, the prevalence of MetS varied between 6% and 7.5% in the intervention group and 10% and 13% in the control group. The intervention group had a 41% lower risk of MetS compared with the control group (relative risk [RR], 0.59; 95% confidence interval [CI], 0.40-0.88; $P = 0.009$). There were no study group-by-sex or study group-by-age interactions, indicating that the interaction effects were similar among females and males at different ages. On the individual MetS components, the intervention decreased risk of high blood pressure in both sexes (RR, 0.69; CI, 0.46-0.98; $P = 0.039$) and high triglycerides in male subjects (RR, 0.71; 95% CI, 0.52-0.98; $P = 0.006$). A study group-by-age interaction on glucose indicated that the effect of intervention was different by age. In pairwise comparisons, the risk for high glucose was lower in intervention participants only at 18 years of age (RR, 0.60; 95% CI, 0.38-0.96; $P = 0.016$). A statistically nonsignificant reduction in waist circumference was measured in the intervention group compared to the control group (RR, 0.78; 95% CI, 0.59-1.03;

$P = 0.09$). The intervention was not associated with positive changes in HDL-C.

■ COMMENTARY

What a study! This is a first of its kind — a longitudinal trial started in infancy to report the effect of repeated dietary intervention/counseling on the risk of adolescent MetS. The big picture ramifications extend to prevention of type 2 diabetes mellitus and cardiovascular disease in adulthood. Talk about preventive medicine! Or, as the investigators brilliantly state, “primordial prevention.”

These are not the first results to be reported from the STRIP study. Earlier analysis found a lower clustering of cardiometabolic risk factors in the intervention group compared with the control group in 5- to 15-year-old participants.¹ Insulin sensitivity was also found improved in the intervention group.² The blood pressure benefits found in this study were also found in the intervention group between the ages of 7 months and 15 years.³ The intervention group had on average 1 mmHg lower blood pressure than the control group.

Early life exposures, including diet, have significant ramifications for future health. Numerous studies have shown that environment and lifestyle (diet and exercise being two keys) are associated with not only childhood obesity and dyslipidemia but also with health outcomes in adulthood that include MetS, type 2 diabetes mellitus, dyslipidemia, hypertension, obesity, and subclinical atherosclerosis.^{4,5} In the Dietary Intervention Study for Children with hypercholesterolemic children, the benefits of a low-fat, high-fiber diet started in childhood on glycemic control were evident in adulthood.⁶

The major strengths of this study are the long follow-up period beginning early in life, the large number of repeatedly studied participants, and the use of well-established measures of MetS. A major shortcoming is the fact that the children in the STRIP study were all white. Also, with such a large dropout rate, an intention-to-treat analysis would have been useful. Hopefully, this remarkable design can be repeated in larger and more diverse populations in the future.

Finally, some good news reported in *The New York Times* on July 26.⁷ Reported by Margot Sanger-Katz, calories consumed in the United States appear to be dropping since they peaked in 2003. Interestingly, the drop in caloric intake appears to be occurring mainly for children. Is the federal government mandate to make school lunches healthier having an effect? One notable fact in the article is that Americans averaged about 40 gallons of full-calorie soda in 1998 and this has “dropped” to 30 gallons in 2014. ■

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PAIN

SHORT REPORT

Music for Postoperative Pain

By David Kiefer, MD

SYNOPSIS: Music, irrespective of type and timing, improves recovery from surgical procedures based on this meta-analysis.

SOURCE: Hoyle J. Music as an aid for postoperative recovery in adults: A systematic review and meta-analysis. *Lancet* 2015; August 13. [Epub ahead of print].

This report may have come to your attention from a recent National Public Radio audio segment,¹ or it's a confirmation of personal experience with the soothing effects of music. Either way, the results are compelling and may positively shape follow-up from one of allopathic medicine's most drastic, and effective, interventions: surgery. In this systematic review, the authors included 73 randomized, controlled trials relevant to the effect of music on recovery from surgical procedures. Inclusion criteria included any form of music before, after, or during a surgical procedure (excluding head/neck, because of potential effect on hearing). With respect to intervention groups, there was a variety of music and delivery used, the latter included such devices as headphones, musical pillows, and background sound systems. The timing and length of treatment also varied between the studies. Control groups included no music, bed rest free from disturbance, and white noise. Table 1 shows the results found; music therapy led to improvements in most categories, including less postoperative pain, anxiety, and analgesic use. These comparisons used a "standard mean difference" due to the fact that many studies used different scales, though the postoperative pain measurement only incorporated studies that used the Visual Analog Scale (VAS), while the anxiety score was based on studies that used the State-Trait Anxiety Inventory (STAI). The increase in patient satisfaction was not statistically significant, nor was the length of stay in the hospital. The type of music used did not affect the findings, nor did the timing of the music "treatment" (one must ask whether it is correct to call listening to music a treatment). Interestingly, music was effective even when patients were under anesthesia.

Summary Point

- Music improves postoperative pain, analgesic use, and anxiety.

Outcome	Standard mean difference compared to control groups (confidence interval)
Postoperative pain (VAS)	-0.77 (-0.99-0.56)
Anxiety (STAI)	-0.68 (-0.95-0.41)
Analgesic use (mg per drug)	-0.37 (-0.54-0.20)
Patient satisfaction (varied scales)	1.09 (0.51-1.68)
Length of stay (varied definitions)	-0.11 (-0.35-0.12)

Provided that the extra sound music contributes to an already busy surgical suite doesn't compromise the ability of staff to hear each other during a procedure, the researchers were quick to point out the safety of music, an intervention apparently free of side effects. How will this change our clinical practice? For those of us involved in surgical procedures, we will be hard pressed not to involve some music, any music, during the pre-operative,

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operative, and postoperative period. The exact type and duration of music does not seem to matter, but given the appearance of other patient-oriented initiatives in the medical system and the connection to improved patient outcomes, perhaps the first step should be “What would you like to listen to today?” ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. Which micronutrient supplement has the best evidence for preventing the development of type 2 diabetes mellitus?
 - a. Alpha-lipoic acid
 - b. Zinc
 - c. Magnesium
 - d. Chromium
2. Which micronutrient supplement has been associated with an increase in all-cause mortality among type 2 diabetics?
 - a. Magnesium
 - b. Alpha-lipoic acid
 - c. Vitamin D
 - d. Zinc
 - e. None of the above
3. Which of the following is true from a recent meta-analysis comparing acupuncture to pharmaceutical use in Alzheimer's disease treatment?
 - a. Pharmaceuticals can cure Alzheimer's disease.
 - b. Acupuncture can cure Alzheimer's disease.
 - c. Acupuncture may enhance the effects of certain pharmaceuticals for symptoms of Alzheimer's disease.
 - d. Acupuncture may cause significant adverse effects in those with Alzheimer's disease.
4. Dietary counseling (including reduction of saturated fats and increased consumption of grains, vegetables, and fruits) from infancy to adolescence was associated with what percentage reduction in risk of adolescent metabolic syndrome compared to a control group?
 - a. 10%
 - b. 25%
 - c. 41%
 - d. none of the above
5. Specific components of metabolic syndrome found to be significantly improved in the dietary intervention group included:
 - a. blood pressure.
 - b. triglycerides (males only).
 - c. waist circumference.
 - d. Both a and b
6. In this meta-analysis, which of the following improved with the use of music during some part of the operative period?
 - a. Patient satisfaction
 - b. Analgesic use
 - c. Length of stay in the hospital
 - d. Number of quarrels in the operating room

[IN FUTURE ISSUES]

Glycemic index and cardiovascular disease

N-acetylcysteine for tobacco use disorder

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