AHC Media

Integrative Medicine

Vol. 18, Issue 10, October 2015
AHCMedia.com

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

DIABETES

ABSTRACT & COMMENTARY

Integrative Therapies for Type 2 Diabetes Mellitus: Botanical Supplements

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

The burden of type 2 diabetes mellitus (T2DM) is staggering. Recent figures estimate that nearly 10% of the U.S. population suffers from T2DM, contributing to $176 billion in direct medical costs and $69 billion in lost productivity.[1,2] Unfortunately, these costs rose by more than 40% over the previous 5-year period.[3] Reversing the epidemic of T2DM will require a patient-centered treatment plan that draws on many different evidence-based therapeutic modalities.

Given that Americans spend approximately $34 billion annually on complementary and alternative medicine,[4] it should not surprise medical providers that one-third of diabetic patients take non-prescription dietary supplements as part of their treatment.[5] Among the various supplements used, botanical remedies consistently rank at the top of surveys.[6,7] Botanicals may serve as effective agents in the treatment of diabetes, as more than 1200 different plants have been reported to have glucose-lowering properties.[8] In fact, metformin, the first choice pharmaceutical treatment for T2DM, originated from the plant *Galega offcinalis* (French lilac).[9] Botanicals have long been used in traditional healing systems across the world and may offer additional treatment strategies for the management of T2DM.

The previous issue of *Integrative Medicine Alert* presents evidence for using micronutrient supplements (chromium, magnesium, zinc, etc.) to manage T2DM.[10] Part two of this review will focus

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, reports he is a consultant for WebMD. Peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and associate managing editor Jonathan Springston report no financial relationships relevant to this field of study.

Integrative Medicine [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Integrative Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

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Summary Points

- More than 1200 different plants have been reported to have glucose-lowering properties.
- Berberine and fenugreek have the best evidence supporting use in patients with type 2 diabetes mellitus.

exclusively on the role of botanicals for treating T2DM. Only recently have rigorous research methods been applied to the study of botanical remedies. Some of the most commonly encountered botanicals used for T2DM are reviewed below.

BERBERINE

Berberine is a plant alkaloid found in several different plants including barberry (*Berberis vulgaris*), goldenseal (*Hydrastis canadensis*), and Oregon grape (*Berberis aquifolium*).[11] Long used to treat bacterial diarrhea in traditional Chinese and Ayurvedic practices, berberine was only recently noted to have antidiabetics properties.[12] Multiple mechanisms for berberine's hypoglycemic effect have been evaluated, including its ability to increase insulin sensitivity, inhibit hepatic gluconeogenesis, and promote intestinal glucagon-like protein-1 secretion.[13]

Although large-scale, randomized, controlled trials are lacking, berberine performs exceptionally well in a number of smaller studies evaluating its use in isolation and in conjunction with traditional diabetic medications. As a primary treatment intervention, 500 mg of berberine twice per day has been shown to significantly outperform placebo in hemoglobin A1c (HbA1c) lowering effect (-0.9% vs -0.3%, respectively).[14] In another randomized trial, berberine at 500 mg three times per day equaled metformin in HbA1c lowering effect (-2.0% vs 1.5%, respectively; $P < 0.05$);[15] however, it should be noted that metformin was sub-maximally dosed at 500 mg three times per day. A systematic review of 14 randomized trials also found that treatments combining berberine with oral hypoglycemic agents achieved better glycemic control compared with oral hypoglycemic agents alone.[16]

The research on berberine has rapidly progressed and the preliminary findings show promise for this botanical in the management of T2DM. Until larger, multicenter studies are performed, berberine might be best considered as an adjunct to traditional oral antidiabtetic medications. Unfortunately, a 1-month supply of berberine is more expensive than most generic antidiabetic medications, ranging from $20-$40. The plant alkaloid is generally well-tolerated, with no reports of hypoglycemic events at the typical dose of 1 g/day. Drug interactions should be considered when using berberine due to decreased activity of several cytochromes (CYP2D6, 2C9, 3A4).[17] Finally, berberine is contraindicated in pregnancy as it may cause uterine contractions.

CINNAMON

Although nearly 250 species of cinnamon have been identified, primarily two species are used to produce the commonly used spice, *Cinnamomum verum* (Ceylon cinnamon) and *Cinnamomum cassia* (Chinese cinnamon). Well-known as a flavoring agent, cinnamon is also sold as a preventive and therapeutic supplement for a variety of chronic medical conditions, including T2DM.[18] The potential antidiabetic properties of cinnamon are believed to result from its ability to increase glucose entry into cells via enhanced insulin receptor phosphorylation and translocation of the glucose transporter to the plasma membrane.[19]

With regard to clinical outcomes, the literature suggests that cinnamon may decrease fasting blood sugar,[20] but it fails to consistently reduce HbA1c levels.[21,22,23,24] A 2012 Cochrane review concluded that there is insufficient evidence to support the use of cinnamon for T2DM.[25] A subsequent meta-analysis

reached a similar conclusion, stating that the high degree of heterogeneity among studies limits the application of any findings to direct patient care.[26] Despite the conclusions of these meta-analyses, randomized, controlled trials do show a HbA1c lowering effect as high as 0.4% when taking 1 g of Chinese cinnamon per day (~ 1/6 teaspoon/day).[27]

Overall, cinnamon falls short of its expectations in the treatment of T2DM. At the present time, patients should be advised against supplementing their diet with cinnamon in hopes of improving diabetic outcomes. With that said, the current literature should not dissuade the liberal application of cinnamon to food if so desired.

FENUGREEK

The seeds of the legume Fenugreek (*Trigonella foenum-graecum*) have been used as both a culinary and a medicinal agent in various cultures around the world. In the Ayurvedic tradition, defatted fenugreek seeds have been used to treat diabetes for centuries. Along with its high fiber content, fenugreek contains 4-hydroxyisoleucine, which increases pancreatic insulin secretion.[28] Additionally, fenugreek is hypothesized to inhibit sucrose α-d-glucosidase and α-amylase,[29] further contributing to its possible antidiabetic effect through slowed carbohydrate absorption.

From a clinical standpoint, the evidence for fenugreek trends toward an overall benefit, although the methodological quality of the various studies is suboptimal. Early studies of small sample size and short duration were mixed in their outcomes;[30,31,32] however, a more sizable and extended trial later found a robust HbA1c lowering effect of 1.4% among fenugreek users compared to 0.4% among placebo users ($P < 0.05$).[33] A recent meta-analysis also noted improvements in HbA1c (-0.85%; 95% confidence interval, -1.49% to -0.22%), but ultimately concluded that higher quality studies are needed to provide more conclusive evidence.[34]

If supported by stronger studies, fenugreek may ultimately serve as an important antidiabetic agent. In the meantime, the botanical still may be recommended for diabetics given its high fiber content, a nutrient known to be beneficial across a variety of disease states. A commonly recommended dose is 2.5 g twice daily of the powdered seed capsulated. Fenugreek may produce a harmless maple syrup smell to urine and has rarely been reported to cause hypokalemia.[35]

GYMNEMA

Gymnema (*Gymnema sylvestre*) is a large, woody plant found in the tropical forests of India, Africa, and Australia.[36] Both the dried leaf and dried root have been used therapeutically in the Ayurvedic system as it causes a loss of sweet taste when chewed. The active constituent of gymnema is believed to be gymnemic acid, a mixture of different saponins; however, a clear mechanism for its glucose-lowering effect has not been determined.[37]

In comparison to the other botanical supplements discussed, gymnema lacks a large body of research to draw definitive conclusions. The two strongest studies found improvements in glucose metabolism as well as a reduction in the use of antidiabetic medications.[38,39] Unfortunately, both studies possessed small sample sizes and lacked randomization. Other commonly referenced studies included type 1 diabetics,[40,41] thereby limiting conclusions for patients with T2DM.

Although the existing evidence for gymnema appears positive, the overall verdict is inconclusive given the scarcity of high-quality data. If consumed, gymnema typically is taken in a capsule or tea form, standardized to 24% gymnemic acids. One case report has implicated high-dose gymnema tea as a cause for acute hepatitis.[42]

IVY GOURD

Ivy gourd (*Coccinia grandis*), also know as baby watermelon, is a perennial herb originally found in India, but has spread rapidly across the world. The antidiabetic mechanism of ivy gourd is not well understood, but the fruit and leaves of the plant appear to have insulin-mimetic properties.[43]

Several studies, including a few randomized, controlled trials, have demonstrated a positive effect of ivy gourd in the management of T2DM. The *British Medical Journal* initially published a small study in 1980 reporting a glucose-lowering effect of ivy gourd when compared to placebo.[44] Subsequently, two open-label prospective trials have also noted a hypoglycemic effect among diabetics consuming ivy gourd.[43,45] More recently, two randomized, double-blind, placebo-controlled trials have been performed and found significant improvements in both fasting and postprandial blood sugars as well as a modest reduction in HbA1c (-0.6%, $P < 0.05$).[46,47]

Although they are mostly single-center studies with small sample sizes, preliminary investigations of ivy gourd are promising, and the herb may be recommended to diabetics with confidence pending more rigorous studies. Unfortunately, dosing recommendations are somewhat difficult

given the different formulations used in each study. No adverse events were reported in the studies reviewed, although they were not specifically designed to identify harm.

OTHERS

Several other botanical supplements, including bitter melon (*Momordica charantia*) and nopal (*Opuntia*), are commonly referenced as having antidiabetic effects. Unfortunately, evidence for these supplements is limited. Two Cochrane reviews have concluded that there is insufficient evidence to recommend bitter melon,[48,49] and the majority of research on nopal is limited to animal models aside from a preliminary study of small sample size (< 20 patients).[50] Although other botanicals may be encountered as well, the supplements with the best available research have been presented above.

CONCLUSION

Historically, botanical preparations have been used to treat hyperglycemia in many traditional healing systems. Driven partly by increased patient use, botanical preparations have been studied more rigorously over the past few decades. Mounting evidence suggests that some of botanicals may be suitable for managing T2DM. The current evidence most strongly supports the use of berberine and fenugreek, with an even stronger recommendation for these botanicals pending larger, multicenter trials. Both ivy gourd and gymnema have demonstrated positive effects in several small studies; however, additional research will be required to recommend these botanicals with confidence. Finally, generally high-quality evidence favors against supplementing with cinnamon for improving T2DM; however, diabetic patients should not be dissuaded from using it liberally as a flavoring agent. Despite these general conclusions, clinicians should bear in mind that the research surrounding botanicals is evolving and should be closely monitored as patients increasingly seek additional treatment options. ■

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ABSTRACT & COMMENTARY

Omega-3s for the AREDS2 Cohort Are Not Beneficial for Preventing Cognitive Decline

By David Kiefer, MD

SYNOPSIS: A sub-analysis of the AREDS2 randomized, controlled trial that involved supplemental omega-3 fatty acids failed to find benefit on cognitive function over 5 years.

SOURCE: Chew EY, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: The AREDS2 randomized clinical trial. *JAMA* 2015;314:791-801.

There is no paucity of the need for interventions to stave off, or treat, cognitive decline as people age. Recent statistics put the worldwide prevalence of dementia at 35.6 million people in 2010, with steep projected increases.[1,2] The authors of this study lead with the sobering fact that the prevalence of dementia in the United States in 2013 was 5.2 million, and it is expected to quadruple in the next 40 years. Pharmaceuticals have a role and efficacy for some, but not all, people. It would seem that omega-3 fatty acid (n-3) supplementation would be a useful intervention, due to some encouraging epidemiological data, a biochemical connection in which docosahexaenoic acid (DHA) is a known constituent of neural tissue, and the fact that low DHA levels have been found in people with Alzheimer's disease. However, this study's authors point out that randomized, controlled trials examining n-3 supplementation have had mixed

Summary Points

- This was a sub-analysis of the AREDS2 research trial, a cohort of 3501 people out of the total 4203 AREDS2 participants.
- A total of 2461 people underwent composite cognition statistical analyses to determine the primary outcome variable, the effect of n-3 supplementation on cognition.
- The authors found that 1 g of supplemental EPA + DHA added to a vitamin supplement for age-related macular degeneration did not prevent cognitive decline.

Table 1: Study Randomization

All patients			
AREDS*	**AREDS minus beta carotene**	**AREDS with low zinc (25 mg zinc oxide)**	**AREDS minus beta carotene and with low zinc (25 mg zinc oxide)**
Then, further randomization			
Placebo	**Lutein/zeaxanthin**	**n-3**	**n-3 plus lutein/zeaxanthin**
1832 people (no n-3)		1909 people (with n-3)	
1235 people included in the composite cognition analysis		1226 people included in the composite cognition analysis	
* AREDS formula = vitamins C, 500 mg; vitamin E, 400 IU; beta carotene, 15 mg; zinc oxide, 80 mg; and cupric oxide, 2 mg			

results for treatment effectiveness. Hence, the current trial, an offshoot of a well-designed clinical trial, was undertaken to shed light on this topic.

The Age-Related Eye Disease Study 2 (AREDS2) (nei.nih.gov/areds2) is a randomized, controlled trial involving 4203 people that was designed to study the effect of n-3 and/or lutein/zeaxanthin in treating age-related macular degeneration (AMD). The study collected data on cognition at baseline and every 2 years, for a mean follow-up of 5 years, so it was thought to be an excellent opportunity to study n-3 supplementation.

People were included in this study if they were at risk of progressing to late AMD, namely, if they had a bilateral large drusen, or one large drusen and AMD in the other eye. After enrollment, people were randomized in a double-masked, placebo-controlled, 2 × 2 factorial design in the following fashion (*see Table 1*): All study participants were offered some version of the original AREDS formula, either original AREDS (vitamin C, 500 mg; vitamin E, 400 IU; beta carotene, 15 mg; zinc oxide, 80 mg; and cupric oxide, 2 mg); original AREDS formulation minus beta carotene; original AREDS formulation with low zinc (25 mg); or original AREDS formulation minus beta carotene and low zinc. The randomization involved n-3 (DHA 350 mg, and eicosapentaenoic acid [EPA] 650 mg) and/or lutein 10 mg plus zeaxanthin 2 mg.

Cognitive function testing consisted of a 30-minute phone survey, thought to correlate well with in-clinic assessments, and used the same cognitive testing as in AREDS, including an abbreviated conglomeration of the Hearing Handicap Inventory, the CES-D (Center for Epidemiologic Studies' Depression Scale), and the TICS (Telephone Interview of Cognitive Status). An additional seven cognitive tests were used, totaling 10, but only eight were used in scoring the overall cognition; it is unclear why the authors excluded two of the tests from the scoring metric. The z scores (a statistical analysis) of each of the eight included tests were combined to make a composite cognition score. The primary outcome was then the yearly change in this composite cognition score; a higher positive score indicated a better result, whereas a higher negative score indicated a worsening of cognition with time. This score ranged from -17 to 22. The authors stated that the study was only significantly powered to analyze n-3 vs no n-3; an assessment of the effect of other nutrients (lutein, zeaxanthin, zinc, beta-carotene) was not statistically possible.

The results were based on original participants who had baseline cognition data, adequate follow-up testing, complete tests, and complete demographic information. The mean age of the participants in the cognition arm of AREDS2 was 72.7 years, and 57.5% were women; the total participants who underwent cognitive testing was 3501, out of the 4203 total AREDS2 participants. Even less of the original cohort had sufficient data and follow-up to allow composite cognition z score calculation; the information from a total of 2461 people underwent such analyses. The baseline composite z score between no n-3 and n-3 groups was 0.4 and 0.3, respectively, with a difference of -0.19 (-0.73 to -0.36; $P = 0.38$), essentially identical. People with higher baseline composite cognition z scores were more likely to be women, white, younger, have a higher income, and were less likely to have hypertension, coronary artery disease, congestive heart failure, myocardial infarction, and stroke. Interestingly, statin use was correlated with a lower baseline composite cognitive z score (-0.1 vs 0.7 for no statin use, $P < 0.001$).

Over the course of the AREDS2 study, cognition declined in all study groups, which was computed as a composite cognition z score change per year during the study period. Addressing the primary

treatment outcome (n-3 effect), the yearly composite cognition z score change was -0.19 (-0.25 to -0.13) and -0.18 (-0.24 to -0.12) in the n-3 and non-n-3 groups, respectively, with an inter-group *P* value of 0.63 (no significant difference). As predicted, due to the under-powered nature of the secondary variables, no statistically significant differences were noted between the groups lutein/zeaxanthin vs lutein/zeaxanthin, high zinc vs low zinc, and beta-carotene vs no beta-carotene.

■ COMMENTARY

It has been difficult to stay abreast of the latest research on n-3s, partly due to the immense quantity of publications on the topic, but also because of the see-sawing of results. The effect of n-3 on cognition exemplifies just that. On one hand are favorable animal studies and mechanistic data,[3] as well as positive clinical trials,[4] but this is then balanced (cancelled out) by the pooling of data into meta-analyses and systematic reviews, which are more lukewarm or cold as to the cause-effect in adults.[5,6]

Does this article help healthcare providers or the general public come to a conclusion about this topic? Possibly. On the one hand, this study has a lot of moving parts and is difficult to interpret. For example, not only is the initial cohort split into four different doses of the original AREDS formula, but then there are four randomly determined groups, two of which are combined to provide the n-3 effect data. The statistical analyses seem adequate, the factorial design organized, but nonetheless it is a dizzying collection of variables. On the more positive side, this is a longitudinal study (5 years), the likes of which are rare to be seen in these days of dwindling research dollars. There is significant attrition, not necessarily perfectly accounted for, but the number of study participants is impressive and lends some credibility to the outcome data provided.

Two more issues relevant to settling the omega-3 cognition issue once and for all deserve mention. The AREDS and AREDS2 cohorts are people with intermediate or late age-related macular degeneration, which may or may not resemble the typical healthcare provider's patient panel. In addition, the sub-cohort analyzed here was predominantly white (+97%) and college to post-college educated, again not reflective of the United States as a whole. There may be few, if any, patients who fit the profile studied in this trial; generalizability is clearly an issue. Furthermore, the n-3 dose deserves tight scrutiny. DHA is the n-3 fraction thought to have the most relevancy to brain physiology, yet was only being supplemented at 350 mg daily. And the total n-3 dose, 1000 mg, is in the realm of the American Heart Association recommendation for secondary prevention of coronary artery disease, but well below the 2-4 g daily of DHA+EPA necessary to treat conditions such as arthritis and hypertriglyceridemia. Was this study underdosed? Possibly, but the ideal n-3 dose is hidden in a wide range of doses used in individual randomized, controlled trials, that melts away with the pooling of data in meta-analyses to which many of us turn for clinical guidance. To further add to this complexity, this study did not detail the study participants' diets, a key component to know the extent to which the n-3 supplementation is actually supplementing.

[This study provides little significant clinical information relevant to the use of n-3 for preservation of cognitive function.]

All told, this study provides little significant clinical information relevant to the use of n-3. Most experts would agree that the dose discussed in this article is safe, carrying a slight "pocket book" adverse effect, but with no benefit for the cohort of people studied here. Let your negotiation with your patients about n-3 use for cognition preservation take precedence over any general clinical guideline until the flaws mentioned above are remedied in the next n-3 study and guide, in a better way, our clinical decision making. ■

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ABSTRACT & COMMENTARY

N-acetylcysteine as Adjunctive Therapy for Therapy-resistant Tobacco Use Disorder

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

SYNOPSIS: Tobacco cessation programs have variable success rates and often employ use of multiple strategies, including behavioral counseling and pharmaceutical treatments. This study investigates the use of N-acetylcysteine in combination with group behavioral therapy as a treatment for tobacco use disorder resistant to first-line smoking cessation treatments.

SOURCE: Prado E, et al. N-acetylcysteine for therapy-resistant tobacco use disorder: A pilot study. *Redox Rep* 2015 Mar 2 [Epub ahead of print].

N-acetylcysteine (NAC), an antioxidant that is a precursor to glutathione (GSH), has been studied for use in a wide range of conditions. Some common therapeutic uses of NAC include intravenous therapy for acetaminophen overdose and as a mucolytic agent for conditions such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and upper respiratory infections.[1] More recently it has become the topic of research for use in a variety of psychiatric conditions including addiction, obsessive-compulsive disorder, depression, bipolar disorder, and schizophrenia with the potential mechanism of action in these realms being via modulating glutamatergic, neurotropic, and inflammatory pathways.[2,3] The use of NAC has been investigated for use in treatment of nicotine, cannabis, methamphetamine, and cocaine addictions, with the hypothesized mechanism of action being function as a glutamatergic agent.[4,5]

Summary Points

- Current smokers diagnosed with tobacco use disorder resistant to first-line therapies were randomized to supplementation with 1500 mg of N-acetylcysteine (NAC) twice daily or a placebo in conjunction with smoking-focused group behavioral therapy.
- The use of NAC in conjunction with behavioral therapy was found to reduce daily cigarette consumption by an average of 10.9 cigarettes a day compared to a reduction of 3.2 cigarettes a day in the placebo group.
- Supplementation with NAC was also observed to reduce levels of exhaled carbon monoxide and improve depression scores measured by the Hamilton Depression Rating Scale.

In this double-blind, controlled trial, 34 current smokers with tobacco use disorder as diagnosed by the DSM-IV criteria were randomized to treatment with a placebo or 1500 mg of NAC twice daily (3000 mg total) for a period of 12 weeks. Study participants were refractory to first-line smoking cessation treatments of nicotine replacement therapy, bupropion, or varenicline, and were involved in a smoking-focused group behavioral therapy before and during the study. The mean pack-years (cigarettes per day times number of years smoking) of the placebo and intervention group were 31.43 ± 18.369 and 32.64 ± 18.519, respectively. Participants ranged in age from 18 to 65 years, and were excluded from the study if they had unstable systemic disease, active gastrointestinal ulcers, were pregnant or breast feeding, or had a history of a reaction to NAC. Individuals were not excluded if they had mood disorders.

The primary outcome of this study was the number of cigarettes per day, evaluated at baseline, 4, 8, and 12 weeks. The secondary outcome measure of smoking reduction was the level of exhaled carbon monoxide (COEX), also evaluated at baseline, 4, 8, and 12 weeks. Breath carbon monoxide levels have been observed in other studies to be related to smoking or non-smoking status, with mean levels in smokers being 17.4 ± 11.6 ppm vs 1.8 ± 1.3 ppm in non-smokers ($P < 0.001$).[6] Additional parameters evaluated were the severity of depression via the Hamilton Depression Rating Scale (HDRS) and body mass index (BMI). Evaluation of outcomes was performed with both a conventional intention-to-treat (ITT) generalized linear model (GLM) analysis with inclusion of all patients who enrolled

in the study, and a modified ITT GLM analysis including patients who had at least one rating 1 month after starting treatment.

Evaluation of the primary outcome of cigarette use per day with the ITT GLM analysis found that the number of cigarettes smoked at the endpoint was significantly lower in the NAC group compared with placebo, with a change in daily cigarettes at the 3-month endpoint of -10.9 ± 7.9 in the NAC-treated group and -3.2 ± 6.1 in the placebo group (P = 0.006). The modified ITT GLM analysis also showed that endpoint daily cigarette use was significantly lower with NAC treatment than in placebo group (Wald = 7.38, P = 0.007). Both the modified ITT and ITT analysis found a significant effect of the baseline number of cigarettes per day.

The secondary outcome of COEX also was significantly lower in the NAC treatment group after 3 months of treatment. With the ITT GLM analysis a decrease in COEX of -10.4 ± 8.6 ppm in the NAC-treated group vs only -1.5 ± 4.5 ppm in the placebo group (P = 0.002) was observed. The modified ITT GLM analysis also found that endpoint daily COEX was significantly lower with NAC treatment than in the placebo group (Wald = 5.60, P = 0.018). Both the ITT and modified ITT analysis showed a significant effect of baseline COEX.

Treatment with NAC also was found to have a significant effect of reducing HDRS score compared to placebo (values not reported in terms of effect). However, there was no significant correlation between the change in HDRS score and the change in number of daily cigarettes smoked or COEX. NAC treatment was observed to have a marginally significant effect of reducing BMI.

Of the 34 individuals who began the study, 10 individuals from the placebo group and six from the treatment group did not complete the study. The reasons for discontinuing included family and social matters (8), referral for other clinical problems (5), and refusal to take medication (3). Two individuals allocated to the NAC group reported an adverse effect of nausea as a reason for discontinuation, while up to six individuals reported symptoms of nausea at the evaluation time points yet did not withdraw from the study. Additional adverse events reported during the study included diarrhea, skin allergy, and respiratory allergy, with the majority occurring in the NAC treatment group, but these events were not significant enough for participants to be withdrawn from the study. No serious treatment-related adverse events were reported.

■ COMMENTARY

Clinical benefits have been seen with NAC as a hepatoprotective agent in settings of acetaminophen overdose and other drug toxicity,[7,8] as an agent that may improve fertility in women with polycystic ovarian syndrome,[9] and as a supportive agent for a variety of mental health conditions.[2] NAC has been shown to be an antioxidant that supports levels of GSH, but also may reduce endothelial dysfunction, inflammation, and fibrosis.[10] Studies investigating the use of NAC in areas of addiction and mental health have hypothesized that the potential benefits seen with NAC are associated with its ability to act as a glutamate modulator.[2]

The use of NAC is the topic of multiple ongoing trials for the treatment of obsessive compulsive disorder, and promising results have been seen in pilot studies.[11] Dosages in those studies are comparable to the current study, ranging from 2400-3000 mg daily for a period of 12 weeks. In other small studies pertaining to nicotine use, NAC was shown to not have an effect on cravings, but decreased the reward associated with cigarette smoking after a period of abstinence.[12] Another small study reported a reduction in cigarettes smoked, and no effect of NAC on CO levels, craving, or withdrawal.[13] In other small addiction studies, the use of NAC was found to decrease the desire to use cocaine[14] and normalize elevated glutamate levels in the dorsal anterior cingulate cortex in cocaine-dependent patients.[15] This is of interest as higher baseline glutamate levels are associated with higher impulsivity and relapse.[16]

In addition to the impact that NAC may have on addictive patterns, GSH is an antioxidant of importance in settings with cigarette smoke exposure. GSH has been shown to be highly concentrated in lung epithelial lining fluid, and levels of GSH in plasma, the liver, and lung epithelial lining fluid have been shown in animal studies to decrease by as much as 50% during an extended period of cigarette smoke exposure.[17] With the potential benefit that NAC has on glutathione levels, endothelial dysfunction, inflammation, and fibrosis, there are many potential mechanisms by which it may have positive impacts on the health of former and current cigarette smokers. As an antioxidant at the level of the lungs and liver, systemically it may help to negate some of the damage done by carcinogens associated with cigarette smoke. It also has been shown to be beneficial as a mucolytic agent improving small airway function and decreasing exacerbation frequency in patients with stable COPD.[18]

There were several limitations of this study. As a small pilot study it does not have a large enough population to appropriately assess safety, efficacy, and effectiveness of NAC as an intervention in this population. There was not a control group without any intervention, as all participants were involved with a smoking-focused behavioral therapy group prior to and during the intervention. Although there was a marginally significant effect of reduction of BMI in the NAC group, this may be attributable to nausea, which was reported as a side effect in up to six participants at the different evaluation points of the study.

[Because its beneficial effects as an antioxidant and for mental well being, NAC may be something to recommend for nicotine cessation.]

Additionally, there was a high dropout rate with 10/17 participants from the placebo group and 6/17 participants from the treatment group not completing the study. Although adverse events of nausea, diarrhea, and respiratory or skin allergy were reported by some individuals in this study, other studies using comparable dosages did not have side effects or effects were mild and transient.[11] Many individuals dropped out for family and social reasons, which may have been due in part to the level of obligation necessary for group behavioral therapy for a 12-week period of time. Generally speaking, the success of smoking cessation intervention therapies has been shown to be greater with more intervention sessions and modalities, and some amount of behavioral motivation or counseling in combination with pharmacotherapy has been shown to be most effective.[19,20] A larger controlled study using NAC without group behavioral therapy or with brief individual motivational counseling during the study would better demonstrate compliance and effectiveness of this as a monotherapy.

This study, similar to other addiction-related studies involving NAC, demonstrates feasibility using NAC in the treatment of addictions. Although adverse effects of nausea were reported in this study, with other studies this was not a significant problem. Gradually increasing the dosage or introducing a small amount of food with a medication are common strategies to reduce nausea, which may be effective with NAC supplementation as well. Because of the beneficial effects of NAC as an antioxidant and for mental well being, it may be something to recommend for individuals interested in smoking cessation. The positive results of this pilot study provides further support for larger population studies with NAC as a supportive agent for nicotine cessation. ■

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ABSTRACT & COMMENTARY

Spice is Nice

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

SYNOPSIS: The habitual consumption of spicy foods is associated with reduced mortality independent of other risk factors for death.

SOURCE: Lv J, et al. Consumption of spicy foods and total and cause specific mortality: Population-based cohort study. *BMJ* 2015;351:h3942.

A group of Chinese investigators conducted a prospective cohort study between 2004 and 2008 and followed 512,891 adults aged 30-79 years until the end of 2013. Participants completed a questionnaire and were divided into four groups based on their reported intake of spices: never, 1-2 days/week, 3-5 days/week, and 6-7 days/week. The spices identified were fresh chili pepper, dried chili pepper, chili sauce, chili oil, and other spices. Ten survey sites were resurveyed in 2008 to confirm the continued intake of spices. Other risk factors for death, such as socioeconomic status, lifestyle behaviors, nutritional intake, presence of chronic conditions, body mass index, fasting blood glucose, and blood pressure, also were measured.

Local health insurance databases were used to determine death and its causes. Seven categories of death were used: cancer, ischemic heart disease, cerebrovascular disease, diabetes mellitus, respiratory disease, infections, and other causes.

The results show that participants who ate spicy foods 6 or 7 days a week showed a 14% relative risk reduction in total mortality compared with those who ate spicy foods less than once a week. Any regular consumption of spices reduced mortality. The reduction was seen in deaths from cancer, ischemic heart disease, and respiratory disease. No associations were significant in the other causes of death. Men and women showed a similar risk reduction.

Summary Point

- Consuming spicy foods is associated with reduced mortality.

■ COMMENTARY

Spices have a long history in the culinary world, and the spice trade is part of the history of civilization. There is a worldwide trend of increased use of spices as flavorings in foods.[1,2] In China, chili pepper is among the most popular spicy foods consumed.

Beneficial effects of spices have been studied, and their bioactive ingredients, such as capsaicin, have been shown to reduce cancer.[2-4] Red pepper has been found to decrease appetite and reduce the rate of overweight and obesity.[5] Spices exhibit antibacterial activity and have an impact on gut microbiota in a way that may reduce the risk of diabetes, cardiovascular disease, liver cirrhosis, and cancer.[6-8]

This study reinforces the emerging science that suggests our nutrition should focus on the wisdom of the ages more than on recent processed foods. Spices have a place among the healthy ingredients of a cuisine. Like with coffee and tea, it is nice when culinary pleasure combines with better health. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **A Cochrane review concluded that there is insufficient evidence to support the use of which supplement for type 2 diabetes mellitus?**
   a. Gymnema
   b. Ivy gourd
   c. Cinnamon
   d. Fenugreek

2. **Which botanical has been shown to have a glucose-lowering effect equivalent to metformin?**
   a. Ivy gourd
   b. Gymnema
   c. Cinnamon
   d. Berberine

3. **Which of the following is true regarding omega-3 fatty acid supplementation in the AREDS2 cohort?**
   a. This positive effect is clearly generalizable, relevant to all people interested in preventing cognitive decline.
   b. Omega-3s were supplemented in food form, such as via extra servings of cold water fish.
   c. The effect was most pronounced on those without age-related macular degeneration.
   d. The omega-3 dose was 1000 mg of EPA + DHA.

4. **In individuals with first-line treatment resistant tobacco use disorder, the use of N-acetylcysteine in conjunction with group behavioral therapy was observed to:**
   a. decrease daily cigarettes smoked, levels of carbon monoxide exhaled, and depression scores.
   b. decrease daily cigarettes smoked and levels of carbon monoxide exhaled, but not change depression scores.
   c. not affect the amount of daily cigarettes smoked and levels of carbon monoxide exhaled, but decreased depression scores.
   d. not affect the amount of daily cigarettes smoked, levels of carbon monoxide exhaled, or depression scores.

5. **Spice intake has been associated with reduced mortality from all of these causes *except*:**
   a. Cancer
   b. Ischemic heart disease
   c. Respiratory disease
   d. Infections

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]

- Acupuncture for hot flashes
- Safety of yoga
- Glycemic index and cardiovascular disease
- CAM use during pregnancy