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OSTEOARTHRITIS

ABSTRACT & COMMENTARY

Chondroitin Is as Effective as Celecoxib for Knee Arthritis

By David Kiefer, MD, Editor

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

SYNOPSIS: Six months of 800 milligrams of pharmaceutical-grade chondroitin sulfate daily relieved knee pain as much as 400 milligrams of celecoxib.

SOURCE: Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: The ChONdroitin versus Celecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis* 2017; May 22. doi: 10.1136/annrheumdis-2016-210860.

The search continues for even partial solutions to symptomatic knee osteoarthritis. Near the top of the dietary supplement list for this is glucosamine hydrochloride (or sulfate), which is usually paired with chondroitin sulfate. Rarely is chondroitin mentioned in its own sentence. That is, until this clinical trial.

In this double-blind trial, 604 people with knee osteoarthritis were randomized to 800 mg of chondroitin sulfate (and a placebo celecoxib capsule; n = 199), 200 mg of celecoxib (and a placebo chondroitin capsule; n = 199), or two placebo capsules (n = 205) for six months. The patients were selected from several European countries, and needed to be older than 50 years of age and with medial or lateral femorotibial compartment arthritis as per the American College of Rheumatology clinical and radiologic criteria. The "target" knee was the side with a greater score on a 0 to 100 visual analog scale (VAS) for pain. Exclusion criteria were referenced from a prior trial (but not detailed in the current study), or having grade 4 knee osteoarthritis, having intra-articular injections in the last six months, taking any dietary supplements for knee pain in the last

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Summary Points

- Researchers randomized 604 people with mild-moderate knee osteoarthritis to 800 mg chondroitin sulfate, 400 mg celecoxib, or placebo for six months.
- Two surveys for pain and function showed similar improvement for the two treatment groups compared to the placebo group, although in one survey the benefits from celecoxib occurred sooner than that from chondroitin.
- Neither of the treatment groups displayed adverse effects more than the placebo group.

three months, taking nonsteroidal anti-inflammatory drugs (NSAIDs) in the last five days, or taking paracetamol in the 10 hours before study enrollment. The primary endpoints were patient VAS pain rating and the Lequesne Index (LI), a pain and function score from 0 to 24. Also, several secondary endpoints were recorded, as were adverse events and abnormal laboratory values. Paracetamol 500 mg tablets were allowed up to a maximum of 3 grams daily for breakthrough pain control.

The authors made a point to draw a stark contrast between pharmaceutical-grade chondroitin, and what is available as a nutraceutical, the latter being less reliable with respect to label claims and product content. They cited more favorable research for pharmaceutical-grade chondroitin, hence the reason for including the form in this research trial. They described pharmaceutical-grade chondroitin as being the 4&6 sulfate form, in no less than a 95% purity.

The researchers completed an intention-to-treat analysis on the 603 patients who actually took the study medication. The demographics between the three groups were similar at baseline, and there were not any significant differences between the dropouts in any of the three groups. For the VAS, all three groups improved compared to baseline at day 30, 91, and 182. Compared to the placebo group, the chondroitin and celecoxib groups improved more than the placebo group, but were similar to each other at six months. (*See Table 1.*) A similar general trend was observed for the LI score, although the celecoxib group reached significance earlier (day 30) than the chondroitin group (day 91) when compared to placebo.

All three groups had the same rate of adverse reactions, most commonly abdominal pain and discomfort. The rate of adverse effects was 2.5% in the chondroitin group, 4.5% in the celecoxib group, and 2.9% in the placebo group.

■ COMMENTARY

This is a favorable study for a dietary supplement for knee osteoarthritis, not always a common outcome in this field. The authors studied chondroitin sulfate, as they described, "… a sulfated glycosaminoglycan composed of chains of alternating D-glucuronic acid and N-acetyl-D-galactosamine." But, this wasn't just your old garden-variety chondroitin; this was pharmaceutical-grade chondroitin sulfate of at least 95% purity. When we send patients to the pharmacy shelves to purchase a dietary supplement, unless you (or they) have checked a third-party certifier's database for accuracy of product content and label claims, our patients may or may not be receiving the necessary bang for their buck. The authors aligned themselves with past research on this pure form of chondroitin to maximize the effect on symptoms of knee osteoarthritis. It appears that their strategy worked.

This study was focused on symptomatic improvement, as documented by the VAS and LI scoring systems, the latter involving both pain and function parameters. The study was considered too short term to capture structural change, so the decision was made not to

Table 1: Chondroitin vs. Celecoxib Visual Analog Scale and Lequesne Index Scores			
	Chondroitin	**Celecoxib**	**Placebo**
VAS (baseline)	71.2	70.0	70.2
VAS (30 days)	49.4	46.9	49.7
VAS (91 days)	39.4	38.3	41.2
VAS (182 days)	28.6 (*P* = 0.001 vs. placebo)	30.5 (*P* = 0.009 vs. placebo)	36.8
LI (baseline)	11.8	11.6	11.8
LI (30 days)	9.6	9.1 (*P* = 0.045 vs. placebo)	9.8
LI (91 days)	8.1 (*P* = 0.050 vs. placebo)	8.0 (*P* = 0.027 vs. placebo)	8.8
LI (182 days)	7.1 (*P* = 0.023 vs. placebo)	7.0 (*P* = 0.015 vs. placebo)	8.0

Results from the two treatment groups and one placebo group for visual analog scale (VAS) pain testing and Lequesne Index (LI) scores for each of the time points. Note: Only the statistically significant *P* values are shown.

analyze for bone nor cartilage markers. Therefore, we don't know whether chondroitin is "building up cartilage" or simply serving as an anti-inflammatory, two of the proposed mechanisms of action. At the end of the day, it may or may not matter, as long as our patients notice some benefit to their symptoms. Does chondroitin sulfate lead to symptomatic improvement immediately, as our NSAIDs of choice might? It is unlikely. In fact, the pharmaceutical in this study, celecoxib, led to benefits in the LI scale a full two months before chondroitin. Not unlike other subtly acting dietary supplements, when we nudge our patients down the chondroitin trail, we encourage them to commit to that treatment in the medium-to-long term, not expecting short-term benefit.

Perhaps this study is the beginning of clinicians considering chondroitin in its own right. Many prior studies examined chondroitin in combination with its more well-known "cousin," glucosamine. Now that we know that a very pure form of chondroitin sulfate also may be efficacious, which one do we choose? Perhaps both. Perhaps what our patient's budget would allow. Perhaps what will be safe with their pharmaceutical list after we consult our resources for supplement-pharmaceutical interactions (which we always should do). Such personalized decision-making should lead, hopefully, to optimal outcomes. And for our patients with symptomatic knee osteoarthritis, there is little reason not to steer them toward a pharmaceutical-grade chondroitin sulfate for at least a three-month trial. ■

HYPERLIPIDEMIA

Bergamot Shows Potential as an Alternative to Statins for Hyperlipidemia

By Ted Wissink, MD, Craig Schneider, MD, and S. Tyler O'Sullivan, DO

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Drs. Wissink, Schneider, and O'Sullivan report no financial relationships relevant to this field of study.

SYNOPSIS: Although larger controlled studies are warranted, bergamot supplementation may be an alternative approach to improving cardiovascular risk in patients who are unable or unwilling to take pharmaceutical HMG-CoA reductase or PCSK9 inhibitors.

The World Health Organization lists cardiovascular disease (CVD) as the No. 1 killer of humans across the globe.[1] Attempts to modify CVD risk factors comprise much of the efforts of both clinicians and the pharmaceutical industry. Along with exercise and dietary modifications, statin drugs (HMG-CoA reductase inhibitors) that modulate lipid metabolism play a major role in reducing mortality from ischemic heart disease. Statins are some of the most frequently prescribed

Summary Points

- Several small human trials with bergamot supplementation have shown significant reduction in total cholesterol, low-density lipoprotein levels, and triglycerides and an increase in high-density lipoprotein levels.
- The main side effect was gastric upset but a small subset of statin-intolerant patients tolerated bergamot well.
- One small clinical trial with bergamot supplementation showed promise for treatment of metabolic syndrome and non-alcoholic fatty liver disease, with a decrease in fasting glucose and a decrease in liver enzymes.

drugs in the United States. Unfortunately, some patients treated with statins still are not able to meet their lipid targets, and up to 15% of patients do not tolerate statins.[2] Adverse effects are more likely in the setting of high-dose statin therapy, advanced age (> 70 years), female sex, renal and hepatic impairment, hypothyroidism, vitamin D deficiency, alcohol abuse, Asian ethnicity, low body mass index, as well as excessive physical activity.[3] Concerns remain about the association between long-term use of statins and diabetes.[4] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are becoming available and may have a great effect, but remain very expensive and are not yet in widespread clinical use.

Alternative agents that modulate lipid metabolism and allow patients to reach their lipid targets in a cost-efficient manner without adverse side effects would be welcomed. Citrus flavonoids have emerged as a promising source of such an agent. Bergamot (*Citrus bergamia*), a member of the Rutaceae family, is found across the Mediterranean region and is widely cultivated in Southern Italy. Fans of Earl Gray tea are familiar with the captivating aroma provided by bergamot. Its essential oil is used in perfumes, cosmetics, and aromatherapy as well. Bergamot juice is obtained from the fruit and is a rich source of flavonoids, including neoeriocitrin, naringin, neohesperidin, C-glucosides, flavone, and flavanone O-glycosides.[5] Flavonoids scavenge free radicals and some varieties, including naringin, act as HMG-CoA reductase inhibitors.[6] Flavonoids appear to modulate various signaling pathways and direct regulation of cellular processes involved in CVD.[7]

CLINICAL EVIDENCE

In a 2016 study, Toth et al enrolled 80 patients (42 male, 38 female), mean age 55 ± 13 years, with moderate hypercholesterolemia (low-density lipoprotein [LDL] 160-190 mg/dL), and never previously treated with statin therapy.[8] Subjects were excluded for severe hepatic or renal disease. All received a daily bergamot-derived flavonoid extract, Bergavit (Bionap, Italy), containing 150 mg of flavonoids (16% neoeriocitrin, 47% neohesperidin, 36% naringin) for six months. Fasting serum (14 hours overnight), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) were collected. LDL cholesterol was calculated (Friedewald formula) at baseline and after six months of Bergavit supplementation. Eleven lipoprotein subclasses also were measured using an FDA-approved diagnostic tool. Additionally, carotid arterial wall thickness was evaluated by color Doppler ultrasound by a single sonographer without access to prior scans.

After six months, there were no significant anthropometric parameter improvements, but TC and LDL decreased significantly. Plasma TC improved from baseline of 257 ± 15 to 223 ± 41 ($P < 0.0001$), a 12% change after six months of supplementation. TG improved from 162 ± 54 to 136 ± 79 ($P = 0.0020$), -17%. HDL improved (increased 8%) from 48 ± 10 to 52 ± 14 ($P = 0.0007$). LDL improved 20% from 176 ± 8 to 144 ± 37 ($P < 0.0001$.) Carotid intimal thickness was reduced from 1.2 ± 0.4 mm to 0.9 ± 0.1 mm ($P < 0.0001$), a 25% reduction in thickness.

The authors concluded that Bergavit may improve the cardiovascular risk profile of patients with moderately elevated hypercholesterolemia by altering the atherogenic lipid pattern, including the increase in large and decrease in small dense LDL particles. LDL reduction was more significant in those subjects with higher baseline plasma LDL-C levels. As this study was not randomized and did not include a placebo arm, conclusions are limited. However, strengths include the favorable tolerability of the bergamot extract and high-quality methodology used to collect the biochemical measurements and carotid intimal thickness. The authors declared no conflicting commercial or financial relationships.[8]

Mollace et al studied the effect of oral bergamot on lipids and blood glucose both in rats and humans.[9] Bergamot was obtained by industrial pressing and squeezing of fruits collected from southern Italy. Standardized capsules were made according to the European community guidelines concerning

dietary supplements. The capsules contained 500 mg of bergamot powder along with 50 mg ascorbic acid. The placebo tablets contained 500 mg maltodextrin supplemented with 50 mg ascorbic acid. The bergamot used contained 26-28% of five main flavonoids.

In the rat study, researchers divided the rats into four groups of 10 rats each. Group 1 was kept on a standard diet for 30 days. Group 2 received a hypercholesterolemic diet for 30 days. Groups 3 and 4 received the hypercholesterolemic diet for 30 days, but each rat was administered bergamot 10 and 20 mg/kg/rat daily. During the 30 days, each rat was weighed daily and 24-hour food consumption was recorded each day. Fecal samples were drawn each day as well. At the end of the 30 days, fasting labs were collected. All rats fed the hypercholesterolemic diet showed elevated TC, LDL, HDL, and TG compared to controls. The bergamot supplement produced significant reduction ($P < 0.01$) in TC, LDL, and TGs (close to a 30% reduction), and no significant difference was found in mean body weight or 24-hour food consumption between the groups receiving bergamot and the controls who were fed the hypercholesterolemic diet without bergamot. The lipid levels were still higher than controls that were not fed the same diet. The fecal output of total bile acids and neutral sterols was enhanced, suggesting the bergamot extract enhances the hepatobiliary turnover and cholesterol consumption. The supplement did not produce any evidence of toxicity in the animal models.

The human study used a randomized, double-blind, placebo-controlled design. Treatment with bergamot 500 mg and 1,000 mg daily (38% flavonoids) for 30 consecutive days in patients with isolated hypercholesterolemia (Group A), mixed hyperlipidemia (Group B), and metabolic syndrome (Group C) led to a strong reduction in TC and LDL, and a significant increase in HDL in the majority of participants. No significant changes were seen in the mean lipid levels in the maltodextrin placebo groups. In particular, the 59 metabolic syndrome participants (Group C) responded very well. In Group C participants receiving the high-dose bergamot, mean TC dropped from 278 mg/mL to 199 mg/mL, mean LDL from 188 mg/mL to 126 mg/mL, and mean TGs from 267 mg/mL to 158 mg/mL. These were all significant reductions ($P < 0.001$). In addition, the metabolic syndrome group showed a highly significant decrease in mean blood glucose. No change in blood glucose was seen for the placebo group. Mollace et al also recruited 32 patients with a history of statin toxicity who had stopped their statins for at least two months before starting a very high-dose 1,500 mg/day bergamot supplement.[9] In this group, 30 of 32 patients responded with a 25% reduction in TC and 27.6% reduction in LDL after 30 days. The study noted no reappearance of statin side effects. For all groups in the study, no differences in liver function were seen, and no side effects were reported, other than mild gastric upset in 9% of patients on the 500 mg supplement and 16% of patients on the 1,000 mg supplement. No patients stopped the supplement because of these side effects.

[Given the prevalence of hypercholesterolemia, metabolic syndrome, and the associated morbidity and mortality with these conditions, it is increasingly important to find ways to treat these conditions.]

Gliozzi et al used a placebo-controlled model to study 107 patients with both metabolic syndrome and non-alcoholic fatty liver disease (NAFLD).[10] There was no mention of blinding for participants or researchers in the study design. The diagnosis of metabolic syndrome was based on having three of the five NCEP-ATP III criteria (abdominal obesity, triglycerides > 150, HDL < 40 for men or < 50 for women, BP > 135/> 85 mmHg, and fasting blood glucose > 110), and the concomitant NAFLD was diagnosed by ultrasound of all patients. Baseline demographic information and alcohol consumption were statistically similar for both the bergamot and placebo groups. The authors conducted face-to-face interviews and physical exams for each participant, although there was no comment on comparing medications taken between participants. Participants were excluded for any excessive alcohol use or history of viral or autoimmune liver disease. Fruits were collected in southern Italy, and bergamot juice was obtained by standard pressing. The study used a standardized 650 mg capsule with 50 mg ascorbic acid and a placebo of maltodextrin 1,000 mg and ascorbic acid 50 mg. The supplements all were made using good manufacturing practices. Fasting labs were collected on the first day and again after 120 days

of treatment with bergamot 650 mg twice daily vs. placebo. All baseline tests showed consistency with metabolic syndrome and NAFLD diagnoses, with mean elevation in body mass index, blood glucose, TC, LDL, TG, and AST/ALT levels.

After 120 days of bergamot supplementation, participants showed a significant reduction ($P < 0.05$) in fasting glucose (118 mg/mL to 98 mg/mL), TC (245 mg/mL to 182 mg/mL), LDL (162 mg/mL to 101 mg/mL), TGs (232 mg/mL to 160 mg/mL), ALT (54 U/L to 36 U/L), and AST (52 U/L to 41 U/L). The participants also showed a significant increase ($P < 0.05$) in mean HDL (38 mg/mL to 49 mg/mL). The researchers also collected high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor (TNF) pre- and post-intervention levels, and found both the mean hs-CRP (1.2 mcg/dL to 0.94 mcg/dL) and TNF-alpha (14.4 pg/mL to 10.7 pg/mL) levels significantly decreased ($P < 0.05$). Moreover, the repeat ultrasound at 120 days showed a significant mean decrease in the hepatorenal index (2.8 to 1.5). These decreases suggest that the metabolic syndrome and NAFLD were accompanied by an inflammatory state and the bergamot supplementation acted to decrease this inflammation.

CONCLUSION AND FUTURE DIRECTIONS

Given the prevalence of hypercholesterolemia, metabolic syndrome, and the associated morbidity and mortality with these conditions, it is increasingly important to find ways to treat these conditions. Diet, exercise, and other lifestyle modifications almost always are recommended first steps, but many patients need additional support in achieving their goals.

For hypercholesterolemia, the most common medications used are statins, but there is still a subset of patients who cannot tolerate these because of side effects or comorbid conditions.[3] Studies from Toth et al[8] and Mollace et al[9] showed bergamot has significant benefit to cholesterol profiles, including decreased LDL and TC, as well as increased cardiac protective HDL. The study by Gliozzi et al showed increased HDL, decreased TC and LDL, as well as decreased inflammatory markers and liver function tests with bergamot supplementation.[10] The main side effect reported in the studies was gastric upset, so patients should be warned about this if they decide to use bergamot.

The Toth et al study was in statin-naïve patients and excluded those with renal or hepatic dysfunction.[8] Future studies could assess tolerance of the supplement in patients with renal or hepatic impairment. The Gliozzi et al study actually showed improvement of liver function tests and no major side effects.[10] The Mollace et al study included a small subset of 32 patients previously exhibiting statin toxicity who then tolerated bergamot supplementation with good results.[9] A larger study could be attempted in the future to further assess tolerance in those patients with prior statin intolerance. Another future study could compare bergamot with red yeast rice, as these both have utility in patients who have not tolerated statins in the past.

RECOMMENDATIONS

These early studies are promising. Bergamot may be an alternative for statin-intolerant patients, but more studies are needed before we can recommend it as first-line or even second-line. The overall tolerance of bergamot with only minimal gastric upset does make it reasonable to consider for statin-intolerant patients, although red yeast rice also is well tolerated and has been studied more extensively. Red yeast rice dosing is 1,200 mg twice daily with meals. Bergamot dosing is 500-650 mg twice daily. ■

REFERENCES

1. World Health Organization. The top 10 causes of death. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed June 1, 2017.
2. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci* 2015;11:1-23.
3. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2889-2934.
4. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735-742.
5. Gattuso G, Barreca D, Gargiulli C, et al. Flaovoid composition of citrus juices. *Molecules* 2007;12:1641-1673.
6. Lee MK, Moon SS, Lee SE, et al. Naringenin 7-O-cetyl ether as inhibitor of HMG-CoA reductase and modulator of plasma and hepatic lipids in high cholesterol-fed rats. *Bioorg Med Chem* 2003;11:393-398.
7. Gonzalez-Gallego J, Garcia-Mediavilla MV, Sanches-Campos S, Tunon MJ. Fruit polyphenols, immunity and inflammation. *Br J Nutr* 2010;104(Suppl 3):S15-27.
8. Toth PP, Patti AM, Nikolic D, et al. Bergamot reduces plasma lipids, atherogenic small dense LDL, and subclinical atherosclerosis in subjects with moderate hypercholesterolemia: A 6 months prospective study. *Front Pharmacol* 2016;6:299.
9. Mollace V, Sacco I, Janda E, et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: From animal models to human studies. *Fitoterapia* 2011;82:309-316.
10. Gliozzi M, Carresi C, Musolino V, et al. The effect of bergamot-derived polyphenolic fraction on LDL small dense particles and non alcoholic fatty liver disease in patients with metabolic syndrome. *Adv Biol Chem* 2014;4:129-137.

ABSTRACT & COMMENTARY

Alzheimer's Prevention: No Harm in 'Forgetting' Vitamin E and/or Selenium

By Ellen Feldman, MD

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

SYNOPSIS: This large-scale study of asymptomatic elderly men reveals no indication that selenium or vitamin E (taken alone or in combination) prevents development of dementia.

SOURCE: Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of antioxidant supplement use and dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). *JAMA Neurol* 2017;74:567-573.

In 1906, Dr. Alois Alzheimer first described "a peculiar disease." It has been more than 100 years since Dr. Alzheimer reported distinct microscopic changes in the brain of patients presenting with progressive memory loss, confusion, and other hallmarks of the disease that today bears his name.[1] In the intervening period, medical science has come to understand more facets of the etiology and progression of dementia in general and in Alzheimer's disease (AD) specifically. Unfortunately, efforts to cure this progressively deteriorating condition remain beyond our reach. Although available medications can slow progression, results are inconsistent and do not change the outcome of the disease.[2] Preventive measures have demonstrated more success — consequently the incidence of AD in developed nations appears to be on the decline. However, there remains concern of AD prevalence reaching worldwide epidemic numbers by 2050, in part because of longer life spans among the population.[3]

Summary Points

- This article presents the results of the largest primary prevention trial in Alzheimer's disease: the Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE.)
- The study began as a seven-year randomized clinical trial and continued with a subgroup of participants as a prospective or cohort study for another seven years.
- All study participants entered as asymptomatic males of at least 60 years of age.
- There were four arms of the study: vitamin E alone, selenium alone, combination of selenium and vitamin E, and a placebo arm. The incidence of dementia was 4.4 % in all arms.

The etiology of AD is multifactorial and complex, including both genetic and environmental stimuli. Although the medical field has been aware of the characteristic neurofibrillary tangles and amyloid plaques in the brains of AD patients since Dr. Alzheimer's time, the role of oxidative stress in the development and progression of AD has been investigated only recently.[4] As results of studies regarding oxidative stress in AD became more compelling, researchers began developing an interest in intervention with potent antioxidant supplements, such as vitamin E and selenium. At the onset of the Kryscio et al study, selenium, which is suspected to be essential for optimal central nervous system functioning, had mixed results from several randomized trials.[5] Vitamin E research was pointing to a role for this agent in slowing the progression of mild cognitive impairment to dementia.[6] However, until this current study's publication, very little was understood about the long-term effects of these two supplements in members of the aging asymptomatic population.

Oxidative stress refers to a process when the ability of the body to neutralize free radicals is reduced, often leading to destabilization on a cellular level and potential tissue and organ damage. Free radicals typically are neutralized by antioxidants — a molecule that chemically reacts with and stabilizes a free radical without itself destabilizing.[7]

Table 1: Selected Results from Study Participants				
	Vitamin E	**Selenium**	**Combined**	**Placebo**
Development of dementia	71 men	78 men	91 men	85 men
Percentage of total	4.0%	4.2%	5.0%	4.6%
Hazard ratio	0.88 (0.64-1.2)	0.83 (0.61-1.13)	1.00 (0.74-1.35)	1 (reference)
P value hazard ratio	0.41	0.23	0.98	NA

The study described here is an offshoot of a larger study that began in 2001 to investigate potential roles of vitamin E and/or selenium in the prevention of prostate cancer. The larger study, known as the Selenium and Vitamin E Cancer Prevention Trial (SELECT), was a double-blind, randomized, clinical study that terminated in 2008, four years earlier than scheduled because of results of a futility analysis and lack of efficacy.[8]

Beginning in 2002, a subgroup of men ≥ 60 years of age were recruited from within the original SELECT participants, eventually reaching an enrollment of 7,540 men. Eligibility for this study, the Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE), included the absence of dementia and the absence of substance abuse at baseline, as well as a negative history of specific neuropsychiatric conditions.

When SELECT ended in 2009, participants were asked to remain on as members of a cohort study for both SELECT and PREADViSE. In this manner, 4,271 men from the original 7,540 PREADViSE participants agreed to stop taking the supplements and participate in annual telephone-conducted, two-tiered memory screens. A protocol including referral to specialists (with medical records requested by the PREADViSE group) or further telephone-conducted screening tests was established to evaluate the presence or absence of AD.

SELECTED RESULTS

Kryscio et al noted that the results of this study are best viewed in context of the circumstances surrounding the methodology; that is, the number of participants from the randomized, clinical trial was reduced almost in half to 4,271 men and became a strictly observational cohort study after the halt of the active clinical trial in 2009. To put the results in perspective, this group conducted sensitivity analyses and several other statistical studies to verify legitimacy of the final numbers. The mean time of supplement use for the group was 5.4 years. The dose was vitamin E 400 IU daily and selenium 200 micrograms daily. (*See Table 1.*)

■ COMMENTARY

This study regarding prevention of AD began as a double-blind, randomized, clinical trial and morphed into an observational cohort study after the original parent study (SELECT), which investigated the effect of antioxidant supplements on prostate cancer, was halted because of both lack of efficacy and the association of vitamin E with increased rates of prostate cancer.[8] With the transition to the observational study, participants were instructed to stop supplement use. Thus, in interpreting the results of the study, it is relevant to recognize that while this is the first study regarding the long-term effect of vitamin E and selenium on prevention of AD, the active use of the supplements did not continue throughout the entire study period. Additionally, it is interesting to note that all participants were at least 60 years of age when beginning the supplement use — it very well may be that earlier and lengthier use would show a different effect.

It is also important to note that all arms of the study had a lower rate of dementia development than would be expected in the general population. According to recent estimates, the risk of AD development among U.S. men between the ages of 65 and 75 years is 9.1-10.2% — considerably higher than the 4.4% found in the study under discussion here.[9] Kryscio et al mentioned that this lower rate of AD overall may have made it more difficult to detect an effect from the supplements. They speculated that the lower rate could be because of the relatively higher level of education in the men recruited as study participants.

Over the past three decades, evidence has accumulated showing that educational level is associated with lower incidences of AD. The cognitive reserve theory postulates that specific life experiences lend resistance to the neuropathological insults involved in the development and progression of AD,

while others have speculated that detecting AD via standard memory and processing screens may be less sensitive in persons with higher intellectual levels at baseline.[10] Participants in this study were well-educated, with slightly more than half holding at least a college degree. Standard AD screens were used for disease detection; there were no imaging studies unless a participant was referred for further testing. Given this combination of factors, underdiagnoses should be suspected.

Another factor to note is that the vitamin E supplement used in this study was in the form of alpha-tocopherol. However, there are eight distinct forms of vitamin E, several of which may be beneficial for health.[11] Recent studies using the standard alpha-tocopherol vitamin E supplement have noted that use of only this single isomer may inadvertently decrease serum levels of other forms of vitamin E and lead to misinterpretation of the overall effect of this vitamin.[12]

It is also important to note that the recommended daily allowance (RDA) for selenium for adults is 55 micrograms;[13] this study dosed 200 micrograms daily. One of the risks of excessive selenium serum concentration involves central nervous system toxicity. Although the tolerable upper limit of selenium at 400 micrograms daily is well above the dosage used in the study, the study dose may have had subtle adverse effects in a vulnerable older population.[13]

Despite the methodological limitations of this study — which in addition to those already mentioned include the recruitment of only male participants and the relatively young age at baseline — it may be that antioxidants in supplement form simply are not neuroprotective or useful in prevention of development of AD. A 2013 meta-analysis looking at dietary forms rather than supplement forms of vitamin E found a 20% lower risk of AD with higher dietary intake of vitamin E as well as lower risks with foods rich in vitamin C and beta-carotene.[14] It may be that dietary intake of antioxidants is the key and that supplements simply do not offer the same benefits as a healthy, vitamin- and antioxidant-rich meal plan.

The results of this study offer providers an opportunity to remind patients of the importance of maintaining a healthy and varied diet. Although the jury remains out on the use of supplements in the prevention of AD in general, there is no indication that either vitamin E or selenium in supplement form is useful in prevention of AD. There remains clear evidence that dietary intake of antioxidants is helpful in maintenance of health in general and in AD prevention as well. ■

REFERENCES

1. Hippius H, Neundorfer G. The discovery of Alzheimers. *Dialogues Clin Neurosci* 2003;5:101-108.
2. Cummings J, Aisen PS, DuBois B, et al. Drug development in Alzheimer's disease: The path to 2025. *Alzheimers Res Ther* 2016;8:39.
3. Prince M, Ali GC, Guerchet M, et al. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res Ther* 2016;8:23.
4. Aliev G, Obenovich ME, Reddy VP, et al. Antioxidant therapy in Alzheimer's disease: Theory and practice. *Mini Rev Med Chem* 2008;8:1395-1406.
5. Vinceti M, Mandrioli J, Borella P, et al. Selenium neurotoxicity in humans: Bridging laboratory and epidemiologic studies. *Toxicol Lett* 2014;230:295-303.
6. Peterson RC, Thomas RG, Grundman M, et al,; Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;352:2379-2388.
7. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. *Int J Biomed Sci* 2008;4:89-96.
8. Kristal AR, Darke AK, Morris JS, et al. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. *J Natl Cancer Inst* 2014;106:djt456.
9. Alzheimer's Association. 2012 Alzheimer's Disease Facts and Figures. Available at: https://www.alz.org/downloads/facts_figures_2012.pdf. Accessed May 15, 2017.
10. Xu W, Yu JT, Tan MS, Tan L. Cognitive reserve and Alzheimer's disease. *Mol Neurobiol* 2015;51:187-208.
11. Schmölz L, Birringer M, Lorkowski S, Wallert M. Complexity of vitamin E metabolism. *World J Biol Chem* 2016;7:14-43.
12. Abdala-Valencia H, Berdnikovs S, Cook-Mills JM. Vitamin E isoforms as modulators of inflammation. *Nutrients* 2013;5:4347-4363.
13. National Institutes of Health. Selenium. Available at: https://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/. Accessed June 12, 2017.
14. Li FJ, Shen L, Ji HF. Dietary intakes of vitamin E, vitamin C, and B-carotene and risk of Alzheimer's Disease: A meta-analysis. *J Alzheimers Dis* 2012;31:253-258.

ABSTRACT & COMMENTARY

MBSR vs. Cognitive Behavioral Therapy for Chronic Low Back Pain

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

SYNOPSIS: Low back pain and functional limitation scores in adults with chronic low back pain improved among those randomly assigned to receive either cognitive behavioral therapy or mindfulness-based stress reduction interventions when compared to usual care.

SOURCE: Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: A randomized clinical trial. *JAMA* 2016;315: 1240-1249.

Mindfulness-based stress reduction (MBSR) is an awareness meditation technique that has been studied for its effects on various health conditions.[1,2] Its practice consists of paying attention to the present moment without judgment.[3] This practice helps cultivate self-acceptance and acknowledgment of thoughts and emotions within the body and mind. Because of the overwhelming data showing its benefit, MBSR has been embraced by hospitals[4] and integrative health practices as an adjunctive treatment of chronic illnesses. However, prior to publication of the study by Cherkin et al, MBSR had not been studied clinically in the treatment of chronic low back pain, one of the most common ailments for which patients seek medical care.

Summary Points

- Researchers randomized 342 patients with chronic low back pain to receive mindfulness-based stress reduction training and yoga, cognitive behavioral therapy, or usual care.
- Participants in both intervention groups showed significantly greater improvement in symptomatology and mental health measures at numerous time points, but did not vary significantly between themselves.
- Both interventions can be helpful for treating symptoms of chronic low back pain, but one intervention may not be significantly better than the other.

In this study, 342 patients in Washington state with chronic low back pain were randomized to receive MBSR training and yoga (n = 116), cognitive behavioral therapy (CBT; n = 113), or usual care (n = 113). The participants were recruited from six cities in Washington through a large integrated healthcare system (Group Health). They ranged in age from 20 to 70 years and were enrolled in the study between September 2012 and April 2014. Participants had to have had back pain that persisted for at least three months to be included in the study.

Participants then were stratified equally between the three groups based on their baseline score on the modified Roland Disability Questionnaire (RDQ), one of the primary outcome measures of the study. The RDQ is a validated and widely used health measure for low back pain. It takes into account any functional limitations patients have because of their back pain. All participants received any medical care they needed, and those randomized to the usual care group received $50. The interventions were comparable in format, length (two hours/week), duration (eight weeks), frequency (once weekly), and number of participants. Participants in both intervention groups were given audio CDs, workbooks, and instructions for home practice.

Interviewers collected outcome survey answers (the RDQ and other measures explained below) by phone at baseline, four weeks, eight weeks, 26 weeks, and 52 weeks. Participants were given $20 per interview.

Primary outcome measures included the RDQ scale and ratings of bothersome pain as measured on a scale of 0 to 10, with 10 representing excruciating and debilitating pain. Secondary outcome measures were Graded Chronic Pain Scale, the Patient Global Impression of Change scale, PHQ-8 for depression, GAD-2 for anxiety, the SF-12 Mental Component Score, medication and opioid use for low back pain, and exercises practiced for three or more days per week.

Results showed significant improvements on primary outcome measures (the RDQ and scale of bothersome pain with $P = 0.04$; relative risk [RR], 1.37; 95% confidence interval [CI], 1.06-1.77; and $P = 0.01$; RR, 1.64; 95% CI, 1.15-2.34, respectively) in the MBSR group compared to usual care. The two intervention groups (MBSR and CBT) were not significantly different in terms of these improvements. Clinically meaningful improvement was defined as a 30% or more improvement from baseline on each primary outcome measure. Significant differences in these measures between MBSR and usual care continued at 52 weeks, with similar RRs to that at 26 weeks.

Analysis of secondary outcome measures (which were measured at all time points except at four weeks) showed that participants randomized to MBSR improved more than those randomized to usual care on the depression and SF-12 Mental Component measures at eight weeks ($P \leq 0.001$ and 0.004, respectively). Those randomized to CBT improved more than those randomized to MBSR on depression at eight weeks and anxiety scores at 26 weeks (a -1.48 between-group mean difference vs. a -2.17 between-group difference at eight weeks, and a -0.68 between-group mean difference vs. a -1.16 between-group mean difference at 26 weeks). These participants also improved more than the usual care group at eight and 26 weeks on all three measures.

Characteristic pain intensity scores differed significantly between groups at all time points — eight, 26, and 52 weeks ($P = 0.002$, 0.04, 0.007, respectively). MBSR and CBT groups showed the greatest improvements in comparison to usual-care group participants at all time points. Self-reported global improvement scores showed greater improvement in the MBSR and CBT groups than the usual care group at 26 and 52 weeks, but did not differ significantly from each other at the other times. No differences were observed for SF-12 Physical Component score or self-reported use of medications for back pain at any time point.

Twenty-nine percent of participants attending at least one MBSR session reported an adverse event (mostly temporarily increased pain with yoga), and 10% of participants attending at least one session of CBT reported an adverse event (mostly temporarily increased pain with progressive muscle relaxation). No serious adverse events were reported. Attrition rates were higher in the intervention groups than in the usual care group (79% of participants in the MBSR group and 81% of participants in the CBT group followed up at week 52 compared to 98% in the usual care group).

■ COMMENTARY

Results of this study showed varied significance between time points, with a trend toward improvement in all groups. Participants in both intervention groups showed significantly greater improvement in symptomatology and mental health measures at numerous time points, but mostly did not vary significantly between themselves. This shows that both interventions can be helpful with treating symptoms of chronic low back pain, but that one intervention may not be significantly better than the other.

It is unclear why results varied between time points. Perhaps this was because of follow-up within the groups and/or participants' ability to practice the skills they were learning. Despite the relatively small size of the study, it was methodologically sound with both a control group and two intervention groups. The study's main limitations were its modest sample size and that participants were a homogeneous population (from the same health group and well educated). Additionally, many participants in the intervention groups were lost to follow-up, limiting conclusions.

Attrition rates in the intervention groups were significantly higher than in the usual care group, likely because of the number of sessions involved in the interventions. Despite this, an impressive part of the results was that the interventions were effective, despite almost half of the participants' lack of completion (51% of MBSR and 57% of CBT participants completed six out of eight sessions). This finding suggests that there is an effect on back pain with just a few MBSR or CBT sessions or that the non-attenders' results were washed out by large improvements in those who attended all sessions. It is not clear if a sub-group analysis was done to further elucidate this finding.

The results of this study are exciting, yet not surprising. The power of MBSR has been well

documented for a variety of medical problems.[1,2,5] Given the trend toward overall improvement in symptomatology for chronic low back pain, clinicians can recommend both MBSR and CBT for this condition. It would work best in patients who are able to attend up to eight weeks of group or one-on-one sessions and may not be suitable for those who cannot commit to a lengthy program, either for lack of time or insurance copays. Both MBSR and CBT provide insight and coping mechanisms for patients suffering with chronic pain and may be used best in conjunction with each other and in conjunction with other pain-relieving techniques, such as epidural steroid injections, acupuncture, chiropractic, and massage.

I have seen positive results from such practices among patients with chronic pain. Given the current opioid overdose epidemic, the trend toward using opioids less, and their side effect profile, it is important that healthcare practitioners gain knowledge in the use and benefit of complementary therapies, such as MBSR, for chronic low back pain. ■

REFERENCES

1. Gotink RA, Chu P, Busschbach JJ, et al. Standardised mindfulness-based interventions in healthcare: An overview of systematic reviews and meta-analyses of RCTs. *PLoS One* 2015;10:e0124344.
2. Simpson J, Mapel T. An investigation into the health benefits of mindfulness-based stress reduction (MBSR) for people living with a range of chronic physical illnesses in New Zealand. *N Z Med J* 2011;124:68-75.
3. Center for Mindfulness in Medicine, Health Care, and Society. Mindfulness-Based Programs. Available at: http://www.umassmed.edu/cfm/mindfulness-based-programs/. Accessed May 20, 2017.
4. Elias M. 'Mindfulness' meditation being used in hospitals and schools. Available at: https://usatoday30.usatoday.com/news/health/2009-06-07-meditate_n.htm. Accessed May 22, 2017.
5. Crowe M, Jordan J, Burrell B, et al. Mindfulness-based stress reduction for long-term physical conditions: A systematic review. *Aust N Z J Psychiatry* 2016;50:21-32.

CME QUESTIONS

1. **As determined by the CONCEPT study, which of the following is true regarding chondroitin sulfate?**
   a. Its effect on knee osteoarthritis is comparable to celecoxib for most time points.
   b. Its improvement of pain is comparable to placebo at 91 days.
   c. Nutraceutical chondroitin appears to be better than pharmaceutical-grade chondroitin.
   d. The effective dose in this study is 400 mg daily.

2. **In human trials, bergamot appears to do all of the following *except*?**
   a. Reduce LDL cholesterol
   b. Increase HDL cholesterol
   c. Reduce total cholesterol
   d. Increase high-sensitivity C-reactive protein

3. **Based on the results of the PREADViSE study, which of the following is true?**
   a. Antioxidants in supplemental form — specifically vitamin E and selenium — are useful in the prevention of Alzheimer's disease only when started at a young age (younger than 60 years of age) and continued for 10 to 12 years.
   b. Among older, asymptomatic males, neither vitamin E alone, selenium alone, or a combination of the two was associated with a reduced risk of Alzheimer's disease.
   c. Vitamin E alone in supplemental form was associated with a statistically significant higher rate of Alzheimer's disease than placebo.
   d. Neither vitamin E alone or selenium alone was associated with a reduced risk of Alzheimer's development; the combination of the two supplements showed a slight reduction in risk when consistently ingested over a several year period.

4. **Mindfulness-based stress reduction may be a useful therapy for chronic low back pain as evidenced by:**
   a. improved self-reported function scores.
   b. decreased pain scores.
   c. higher anxiety rating scores.
   d. Both a and b

[IN FUTURE ISSUES]

Lifestyle and physical activity for atherosclerosis

Yoga for low back pain

Exercise and depression in children

Saffron for depression