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DIABETES

ABSTRACT & COMMENTARY

The Role of Ginger in Type 2 Diabetes Mellitus

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

SYNOPSIS: Ginger supplementation exhibits a promising effect on glycemic control, triglyceride levels, and systemic inflammation in type 2 diabetics.

SOURCE: Arablou T, et al. The effect of ginger consumption on glycemic status, lipid profile, and some inflammatory markers in patients with type 2 diabetes mellitus. *Int J Food Sci Nutr* 2014;65:515-520.

Traditionally, the management of type 2 diabetes mellitus involves achieving enhanced glucose control as a result of increasing insulin resistance. However, mounting evidence suggests that insulin resistance, and its associated defects in glucose and lipid metabolism, is just one of the many consequences of chronic, low-grade systemic inflammation.[1] As a result, reducing levels of chronic systemic inflammation has become a growing interest among researchers, especially as it relates to insulin resistance and metabolic syndrome.

Botanicals with strong anti-inflammatory properties routinely generate attention for a possible role in the management of diabetes mellitus. Ginger (*Zingiber officinale*), a spice used in Chinese and Ayurvedic traditions to treat diseases ranging from gingivitis to asthma,[2] contains many antioxidant compounds believed to exert strong anti-inflammatory effects through the inhibition of cyclooxygenase, inducible nitric oxide synthase, and lipoxygenase, as well as through the suppression of prostaglandin synthesis.[3] To assess both the anti-inflammatory properties and

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Summary Points

- Taking 1600 mg of ginger root daily for 12 weeks improves several markers of glucose control (fasting blood, sugar, hemoglobin A1c, and insulin levels).
- Patients with non-insulin dependent diabetes who ingested ginger root had significant reductions in the inflammatory marker C-reactive protein after 12 weeks.

clinical outcomes of ginger supplementation among diabetic patients, researchers in this study developed a randomized, double-blind, placebo-controlled trial to analyze changes in inflammatory markers, glycemic indices, and lipid profiles.

Diabetic patients treated with oral hypoglycemic agents who had a hemoglobin A1c (HbA1c) between 7-10%, as well as a body mass index (BMI) between 20-35 kg/m^2, were recruited for study participation. Exclusion criteria included current pregnancy or lactation, active infection, history of cancer, current tobacco or alcohol use, and/or a renal, liver, thyroid, or parathyroid disorder. Seventy patients initially were enrolled and randomized to consume either 1600 mg capsules of powdered ginger rhizomes or wheat flower placebo daily for 12 weeks (one 800 mg capsule before lunch and one 800 mg capsule before dinner). Ginger was sourced from a local market and both sets of capsules were prepared by the research group. Patients were instructed not to change their diet or activity patterns during the study period and were assessed using a 24-hour recall questionnaire at the beginning and end of the study. Fasting blood samples were also collected at the beginning and end of the intervention and analyzed for blood glucose levels, insulin levels, HbA1c, triglycerides, total cholesterol, and HDL as well as prostaglandin E2 (PGE_2), tumor necrosis factor-alpha (TNF_α), and C-reactive protein (CRP).

A total of 63 patients completed the study (33 in the ginger group and 30 in the placebo group). Several dropouts occurred due to unwillingness to participate, along with one developed pregnancy and one insulin start. Results were analyzed from those completing the study with no reported intent-to-treat analysis. Baseline characteristics, including age, body weight, duration of diabetes, gender, and physical activity, did not differ between the intervention and placebo groups. Analysis of caloric consumption, macronutrients, micronutrients, and dose of oral diabetic medication did not differ before or after the intervention between or among the treatment and placebo groups.

With regard to the primary outcomes, all glycemic indices demonstrated a significant improvement in the ginger group (fasting plasma glucose [FPG], -9.1 ± 38.5 mg/dL, P = 0.02; HbA1c -1.0 ± 1.7%, P = 0.001; insulin -3.7 ± 8.2 µU/mL, P = 0.01) compared to the placebo group (FPG, 16.0 ± 48.5 mg/dL, P = 0.02; HbA1c 0.4 ± 1.4%, P = 0.001; insulin 0.1 ± 3.5 µU/mL, P = 0.01). Among lipid parameters, triglycerides, total cholesterol, and the HDL/total cholesterol ratio were the only measures to improve with ginger supplementation compared to baseline (-45.4 ± 69.6 mg/dL, -15.4 ± 34.3 mg/dL, and 0.2 ± 0.05, respectively). Placebo demonstrated no significant benefit with the lipid profiles. With regard to inflammatory markers, both CRP and PGE_2 levels decreased significantly among ginger users compared to placebo (CRP: -2.5 ± 4.7 mg/L vs -0.7 ± 6.5 mg/L, P = 0.02; PGE_2: -126.7 ± 231.6 pg/mL vs -21.4 ± 60.4 pg/mL, P = 0.009). No changes in weight or BMI were noted with either group.

■ COMMENTARY

Given the overall paucity of data pertaining to ginger in the management of type 2 diabetes, the authors of this study attempted to identify potential changes in inflammatory markers, glycemic indices, and lipid profiles after 12 weeks of supplementation. Improvements were most convincingly noticed in the areas of glycemic control and triglyceride lowering, with data supporting a possible anti-inflammatory effect. Both HBA1c and insulin levels decreased, suggesting ginger may decrease insulin

resistance and decrease serum glucose levels. Ginger is speculated to decrease serum glucose levels through the activities of phenols, polyphenols, and flavonoids, which may inhibit intestinal glucosidase and amylase enzymes.[4-5] The antioxidants within ginger, including paradol and zingerone, might increase insulin receptors and enhance ß-cell function,[6] thereby decreasing insulin resistance. At the moment, the literature surrounding ginger and glycemic control is mixed; however, other studies also have demonstrated positive results when using higher ginger doses of 3 g/day.[7-8]

The effect of ginger on blood lipids is also mixed, as one study demonstrated a decrease in serum triglycerides without an effect on total cholesterol levels,[6] but another study of diabetics with and without coronary artery disease found no significant change in lipid chemistries.[9] A proposed mechanism for the triglyceride-lowering effect surrounds an increase in lipoprotein lipase enzyme activity.[10] Finally, the current study demonstrated a potential anti-inflammatory effect of ginger, primarily through the reduction of CRP — reductions in TNF_{α} were not statistically significant and the wide standard deviation in PGE_2 reductions complicates conclusions. A more robust analysis of inflammatory markers could have enhanced the anti-inflammatory analysis of ginger supplementation. The potential anti-inflammatory effect of ginger should be explored further, given the implications for improving the many complications of metabolic syndrome.

Overall, the study was well-designed with only a few minor limitations that were not explicitly discussed. As previously indicated, an intent-to-treat analysis was not performed, which would have enhanced the validity of the results, as dropouts were not taken into account. Although the patients enrolled in the current study represent the average diabetic patient, those with diabetic nephropathy were excluded, which may limit the findings to patients with poorly controlled or long-standing diabetes. Another important group excluded were those taking insulin, which limits the current recommendations for ginger supplementation among this subset of diabetic patients. Unfortunately, the oral antidiabetic medications taken by the patients were not presented; however, no differences between the groups were reported, thereby reducing the chance that differences were attributable to pre-existing antidiabetic medications. Finally, the duration of this study, as well as others, currently does not extend beyond 3 months, limiting definitive recommendations for long-term use.

Despite its various limitations, the present study suggests that ginger may indeed have a role in the management of diabetes mellitus, particularly among non-insulin dependent diabetics. Although studies have not specifically evaluated harm among diabetic patients, ginger supplementation is generally regarded as safe by the FDA, with a theoretical risk of bleeding that may be amplified with concurrent use of anticoagulant and antiplatelet drugs.[11] Supplementation with ginger root is relatively affordable, with the cost of a 90-day supply averaging about $6 based on a recent Web search. Perhaps the best advice for diabetic patients would be to use ginger several times per week when preparing food or adding it to water, as ¼ teaspoon is roughly equivalent to the dosage studied. ■

[Despite the various limitations, the present study suggests that ginger may indeed have a role in the management of diabetes mellitus, particularly among non-insulin dependent diabetics.]

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ABSTRACT & COMMENTARY

Treatment of Small Intestinal Bacterial Overgrowth with Botanical Therapies Equivalent to Rifaximin

By Carrie Decker, ND

Founder and Medical Director, Blessed Thistle, Madison, WI

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

SYNOPSIS: Small intestinal bacterial overgrowth (SIBO) is a condition associated with symptoms of irritable bowel syndrome and extraintestinal manifestations. This study investigates the effectiveness of the antibiotic rifaximin compared to botanical combination therapies for the treatment of SIBO as diagnosed by lactulose breath testing.

SOURCE: Chedid V, et al. Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. *Glob Adv Health Med* 2014;3:16-24.

The expansion of intestinal microbiota from the predominant location in the colon to the small intestine has been studied as one cause of irritable bowel syndrome (IBS).[1] The population of microbiota in the small intestine creates gas as a byproduct of fermentation, leading to typical IBS symptoms, and may activate host mucosal immunity, leading to a wide array of systemic symptoms. Lactulose is not absorbed or used by the gastrointestinal tract in humans, and is metabolized by bacteria into hydrogen and methane gas. The amount of gas produced can be measured by a lactulose breath test (LBT) and is a common procedure for diagnosis of small intestinal bacterial overgrowth (SIBO).[2] Rifaximin, an antibiotic with little to no systemic absorption, is the most commonly used antibiotic for the treatment of SIBO.[3] Many individuals with IBS seek integrative treatment options, but the use of botanical antimicrobials and other oral supplements is common yet not well studied for effectiveness.[4]

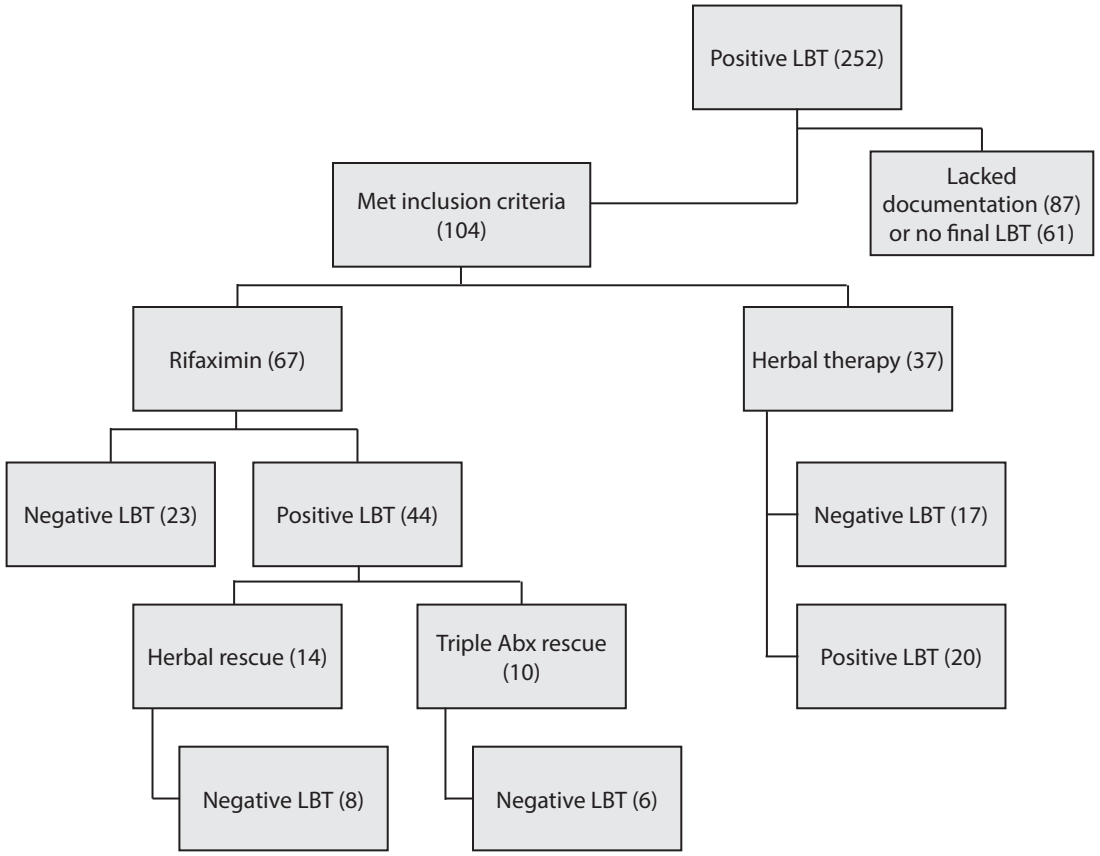
Summary Points

- A retrospective chart review of 104 patients undergoing treatment for small intestinal bacterial overgrowth (SIBO) with a 30-day course of rifaximin or herbal antimicrobials found that herbal treatments were at least equally effective to rifaximin for the treatment of SIBO.
- Herbal antimicrobial combination therapies were similarly effective to triple antibiotic therapy in resolving rifaximin-refractive SIBO.
- Adverse effects were more common and severe in individuals treated with rifaximin.

In this retrospective case review, 104 individuals with SIBO symptoms and diagnosis via a positive LBT were treated for SIBO, including a post-treatment LBT. Symptoms suggestive of SIBO included abdominal discomfort, cramping, bloating, flatulence, eructation, diarrhea, symptoms worsened via food consumption, and low serum B12. Exclusion criteria included patients < 18 years of age or > 85 years of age and antibiotic use within 3 months. A subset of 24 patients who had completed initial treatment with rifaximin and were still found to have a positive LBT were further investigated for response to either herbal or triple antibiotic therapies. (*See Figure 1.*)

Patients were treated for SIBO with rifaximin or herbal antimicrobial protocols based on individual treatment preference. Sixty-seven patients completed treatment with rifaximin and 37 completed treatment with herbal therapies. The herbal products used were the commercially available products Dysbiocide and FC Cidal (Biotics Research Laboratories) or Candibactin-AR and Candibactin-BR (Metagenics). The herbal products were taken at a dosage of two capsules each twice daily. Rifaximin was dosed at two 200 mg tablets three times daily (total 1200 mg/day). Each treatment was for 4 consecutive weeks with a follow-up LBT upon completion. Rifaximin non-responders were further treated by one of the herbal protocols or a triple antibiotic protocol (clindamycin 300 mg, metronidazole 250 mg, and neomycin 500 mg each three times daily) for 4 additional weeks. (*See Table 1.*)

Figure 1: Retrospective Case Review



Of the patients completing treatment with rifaximin, 23 of 67 (34%) were found to have a negative LBT with follow-up testing compared to 17 of 37 (46%) of those receiving herbal therapies ($P = 0.23$). The odds ratio of having a negative LBT after treatment with herbal therapies compared to rifaximin was 1.63 (confidence interval [CI], 0.72-3.70; $P = 0.24$) and 1.85 (CI, 0.77-4.41; $P = 0.17$) after adjustment for age, gender, SIBO risk factors (such as known gastrointestinal motility disorder or chronic proton-pump inhibitor use), and IBS status (diagnosed by Rome III criteria). These comparisons show equivalency.

Fourteen of the individuals not responsive to rifaximin treatment were offered herbal therapies, with 8 of 14 (57.1%) having a negative LBT after herbal treatment, while 10 of the individuals non-responsive to rifaximin were offered triple antibiotics with 6 of 10 (60%) having a negative LBT after triple antibiotic treatment ($P = 1.0$). The population of individuals non-responsive to herbal therapies was not investigated for response to further treatments. The effect of treatments on symptoms was not assessed at completion of treatment.

There was no significant difference in age, gender distribution, IBS-subtype distribution, or risk factors for SIBO in the populations completing treatment with rifaximin vs herbal therapies. However, there was a higher percentage of females than males in both groups (71% in the rifaximin arm and 78% in the herbal arm).

Adverse effects were reported in six individuals in the rifaximin treated arm, including one case of anaphylaxis, two cases of hives, two cases of diarrhea, and one case of *Clostridium difficile* (post-treatment). One case of diarrhea (non-*C. difficile*) was reported in the herbal therapy arm. The rates of adverse effects were not analyzed statistically. This study did not assess the number of study dropouts from the two arms separately. Initially 252 individuals with a positive LBT were recommended treatment but only 104 both completed the treatment protocol and had a follow-up LBT. Of the individuals who did not complete both treatment and a follow-up test, 87 individuals lacked proper documentation of treatment and 61 did not have a follow-up LBT.

■ COMMENTARY

IBS is a common condition, with most prevalence estimates in North America ranging from 10-15%.[5] IBS is often seen to be chronic or recurrent in individuals who experience it. Individuals with IBS report lower (worse)

Table 1: Herbs in Commercially Available Products

FC Cidal	Dysbiocide	Candibactin-AR	Candibactin-BR
• Amrita (*Tinospora cordifolia*) • Horsetail (*Equisetum arvense*) • Pau D'Arco (*Tabebuia avellanedae*) • Thyme (*Thymus vulgaris*) • Tarragon (*Artemisia dracunculus*) • Bala (*Sida cordifolia*) • Olive leaf (*Olea europaea*)	• Dill seed • *Stemona sessilifolia* • Wormwood (*Artemisia absinthium*) • Pulsatilla (*Pulsatilla chinensis*) • *Brucea javanica* • Quassia (*Picrasma excelsa*) • Catechu (*Acacia catechu*) • Damiana (*Hedyotis diffusa*) • Yarrow (*Achillea millefolium*)	• Thyme (*Thymus vulgaris*) • Oregano (*Origanum vulgare*) • Sage (*Salvia officinalis*) • Lemon balm (*Melissa officinalis*)	• Coptis root (*Coptis chinensis*) • Indian barberry (*Berberis aristata*) • Berberine sulfate • Chinese skullcap (*Scutellaria baicalensis*) • Philodendron bark (*Phellodendron chinense*) • Ginger (*Zingiber officinale*) • Chinese licorice (*Glycyrrhiza uralensis*) • Chinese rhubarb (*Rheum officinale*)

health-related quality of life scores than individuals with gastroesophageal reflux disease, asthma, and migraines.[6] SIBO has been increasingly of interest as a contributor to symptoms of IBS,[7] thereby leading to many investigations of the use of antibiotic therapies for treatment.

The LBT is one of the primary tools used to evaluate for the presence of SIBO,[8] and results have shown relationships with IBS. A recent meta-analysis showed the prevalence of a positive LBT of 54% (95% CI, 32%-76%) in individuals with IBS.[9] Odds ratios for a positive LBT in individuals meeting the criteria for IBS range from 3.45 to 9.64 when compared to healthy asymptomatic controls.[9,10] The treatment and resolution of a positive LBT finding is associated with improvement in symptoms of IBS.[11]

Counter to this, a study comparing the amount of bacteria cultured from a small intestinal biopsy (the gold standard for diagnosis of SIBO) have found poor correlation with LBT hydrogen and methane results.[12] Although various markers from the LBT are evaluated for the diagnosis of SIBO, the findings of this study showed a sensitivity of 0 to 33% depending on which parameter was assessed. A positive biopsy finding indicating the presence of SIBO is when ≥ 10 CFU/mL bacteria are present when cultured. One explanation for this discrepancy is that a bacterial culture is a poor environment to stimulate the small intestinal environment, and in vivo the microbial balance may be far different. However, it does shed light on the fact that there is possibly significant error in LBT for the diagnosis of SIBO.

Other studies have evaluated the use of rifaximin as a therapy for patients with SIBO, as demonstrated by positive LBT. Standard dosing strategies are between 1200 mg/day and 550 mg three times a day for 10-14 days.[13] Rifaximin lacks FDA approval for the treatment of SIBO and therefore is costly, ranging from $600-1250 per month. Other antibiotics that have been studied for the purpose of treating SIBO include neomycin, tetracycline, amoxicillin clavulanate, metronidazole, and fluoroquinolones.[14]

This study had some limitations, in addition to the major methodological flaw that it was a retrospective chart review with self-selected treatment choices rather than a double-blind, randomized, controlled trial. Although this study provided a general look at the treatment of SIBO with herbal antimicrobials and saw positive results compared to rifaximin, the results did not distinguish the success rate with the two different herbal antimicrobial protocols. The herbal antimicrobials each were comprised of more than four different herbs with known antimicrobial effects, but there were very little similarities in the formulations.

There also was no report of whether symptoms associated with SIBO were resolved at the end of the treatment course, or if the individuals treated were able to maintain a symptom-free/negative LBT status after discontinuing rifaximin or herbal antimicrobial treatment. A high recurrence rate of SIBO has been demonstrated, with rates of 12.6%, 27.5%, and 43.7% at 3, 6, and 9 months, respectively, after successful (breath test negative) treatment with rifaximin for 1 week.[15] Another study found that after a 14-day treatment course with rifaximin, IBS-associated symptoms (including bloating, flatulence, diarrhea, and pain) were improved for a period of 3 months after treatment.[16] The 30-day treatment course with rifaximin used in the study was longer than in both of these studies, and it is unclear if the longer treatment duration would be more effective in reducing recurrence rates.

Additionally, the positive findings of the lactulose breath test did not distinguish whether positive findings were

due to elevated hydrogen, methane gas, or both. It has been observed that constipation-type IBS is associated with methanogens and is more difficult to resolve with rifaximin.[17,18] Rifaximin has been studied more extensively for the treatment of non-constipation type IBS.[19] Significant improvements in constipation-type IBS have been seen with neomycin,[20] one of the triple antibiotics used in individuals who did not have a negative LBT after rifaximin treatment. The combination of neomycin with rifaximin has been shown to be most effective for normalization of a high methane-positive LBT.[21]

The authors did not state whether other diseases that may have similar gastrointestinal symptoms had been ruled out in the participants in this study. The symptoms suggestive of SIBO (abdominal discomfort, cramping, bloating, flatulence, eructation, diarrhea, symptoms worse with eating, and low serum B12) also may be symptoms of conditions such as celiac disease or inflammatory bowel disease. Although the positive LBT has been shown to demonstrate SIBO, there may be other underlying problems in individuals non-responsive to treatment, or the LBT can be a false positive.

Finally, the authors did not note whether participants followed specific dietary interventions that are commonly recommended for individuals with IBS or SIBO. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is commonly recommended for individuals with IBS and has been shown to have efficacy in the reduction of symptoms,[22] while a high FODMAPs diet has been shown to affect the amounts of breath hydrogen and methane.[23] Individuals who are motivated to seek treatment for IBS often follow gluten-free or dairy-free diets, or diets with low amounts of starch and complex sugar-sourced carbohydrates. The use of other treatments also was not controlled in the study participants. Supplement and over-the-counter medication use is common among individuals with IBS and includes probiotics, digestive enzymes, and antidiarrheal or laxative agents.

Overall, this study was the first to compare the use of rifaximin to herbal antimicrobials for the treatment of SIBO. However, as it is not a prospective study and many variables that may have had an effect were not controlled, it is difficult to come to a clinically relevant conclusion. That said, as adverse effects were minimal with herbal treatments, and resolution of a positive LBT test was found to be equivalent with both therapies, if individuals are interested in using botanical treatments for this purpose, there is no evidence to indicate that this should be discouraged. Further investigation of the efficacy of herbal antimicrobials and a 30-day treatment course of rifaximin that addresses the aforementioned items will offer further insight into what may be most effective for the treatment of SIBO and prevention of IBS recurrence. ■

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ABSTRACT & COMMENTARY

Manipulating Degenerative Joint Disease: RCT Shows Short-term Effects

By David Kiefer, MD

SYNOPSIS: Men with low back pain who received one high-velocity, low-amplitude spinal manipulation had less pain and improvements in disc space and hip and spinal flexion.

SOURCE: Vieira-Pellenz F, et al. Short-term effect of spinal manipulation on pain perception, spinal mobility, and full height recovery in male subjects with degenerative disk disease: A randomized, controlled trial. *Arch Phys Med Rehabil* 2014;95:1613-1619.

Spinal manipulation, practiced most commonly by osteopathic physicians, physical therapists, and chiropractors, has been studied for its effect on low back pain of various etiologies. The researchers of this trial attempt to add to the literature on spinal manipulation, which they claim is "sparse" and "conflicting," through this randomized, controlled trial. In addition, their methodology aimed to determine a mechanism of action, or "neural mechanosensitivity response," through straight leg testing.

The particular type of spinal manipulation examined in this trial is a high-velocity, low-amplitude (HVLA) approach, with thrusts of movement that characteristically create a "pop" to move a specific joint. The researchers randomized 40 men with low back pain to either one HVLA treatment (n = 20) or a control treatment (n = 20), the latter involving similar positioning and time of treatment with no thrust delivered. The men had to have low back pain of category 1 or 2 severity as per Quebec Task Force classification, and magnetic resonance imaging (MRI) of intervertebral disc degenerative in the lumbosacral region. There was a long list of exclusion criteria (*see Table 1*). The immediate effect of the HVLA was evaluated by measuring study participant's height (an indirect indicator of intervertebral disc space), self-perceived low back pain, neural mechanosensitivity as determined by passive straight leg raise range of motion, spinal flexion mobility (forward bend, "finger-to-floor" measurement, with a lower number meaning closer to the floor), and a stadiometer to measure intervertebral disc compression. A stadiometer is a device that can accurately measure height, and by default, changes in height that could be accounted for by intervertebral disc changes; it uses metal bars ("fixing bars") to stabilize certain anatomic points and safety glasses with a built-in leveling system.

The HVLA treatment is called a "pull-move" and was done with the participant in the side-lying position. In the research paper, a photograph was provided showing the position, and references directed readers to past studies using the technique. The HVLA treatments were delivered by one "therapist" (also referred to as a "care provider"), but the researchers did not specify the therapist's training or background. The treatments were delivered in a double-blind fashion, but the exact meaning of this in the context of a hands-on therapy was not discussed.

The treatment and placebo groups were similar at baseline with respect to age, weight, height, low back pain as per a visual analog scale, stadiometry, and spinal

Summary Points

- This randomized, controlled study examined the use of high-velocity, low-amplitude spinal manipulation in 40 men with low back pain from degenerative disc disease.
- After one high-velocity, low-amplitude thrust, men in the treatment group had a statistically significant improvement in pain, disc space, and hip and spinal flexion.

Table 1: Exclusion Criteria

- Smoking
- Alcoholism, or alcohol consumption within 24 hours of data collection
- Professional athletes
- Disc herniation
- Cauda equina syndrome
- "General contraindications" to spinal manipulation (not specified)
- History of surgery for degenerative joint disease
- Radiculopathy
- Recent (within 3 months) spinal manipulaiton

Table 2: Pre- and Post-intervention Measurements of Study Variables for Control and Treatment Groups

	Control Group		Treatment Group	
	Pre-intervention	**Post-intervention**	**Pre-intervention**	**Post-intervention**
LBP (mm on a visual analog scale)	29.0	29.1	37.1	20.0
Straight leg raise (in degrees)	48.0	47.6	39.1	52.8
Spinal flexion (in cm)	9.9	9.6	14.0	10.4
Stadiometry (in mm)	-0.007	0.02	-0.007	3.98

flexion. At baseline, the treatment group had less degrees of range of motion on straight leg testing than the control group (39.10 vs 48.05, respectively, $P = 0.004$).

Pre- and post-intervention, there were no differences in the study variables in the control group. In contrast, all of the post-treatment measurements in the treatment group were statistically different when compared with pre-treatment ($P < 0.001$) (*see Table 2*). When the control group was compared to the treatment group, all study variable differences were statistically significant ($P < 0.001$). Essentially, these results showed that one HVLA treatment improved low back pain (lower score on the visual analog scale), increased hip range of motion (more degrees on straight leg raise testing), improved back flexibility (fingers closer to the floor on forward bend), and widened intervertebral disc space as per stadiometery. There were no dropouts in this trial. Adverse effects were not discussed.

■ COMMENTARY

This trial appears to be a vindication of spinal manipulation for the short-term relief of low back pain due to a degenerative disc disease etiology, corroborating some reviews.[1] And, for many people who have otherwise maxed out pharmaceutical therapy, physical therapy, and corticosteroid injections, these results seem to be, well, a welcome relief. However, in many respects, these findings are nothing new; clinicians and patients alike can attest to the fact that spinal manipulation leads to initial benefits, which, in this physician's professional experience, often wane with time. More compelling would have been a longitudinal study to examine the duration of benefit or a series of arms to elucidate how it would be possible to make the initial benefits last longer; for example, perhaps spinal manipulation paired with physical therapy is the key to provide instant relief, followed by musculoskeletal stability that maintains the positive changes measured in this clinical trial.

The researchers do bring some important nuances to the low back pain table. For example, their study variables hint at a mechanism of action. The measurements seem to indicate that HVLA opens the intervertebral disc space at the target joint and improves the straight leg raise testing, possibly an indication of, in their words, "neurodynamics of lower extremity posterior muscles and neural structures." They extrapolate this finding to possible inhibitory effects on motor neurons and improved mechanosensitivity, both of which would have to be corroborated with more extensive neurological testing. As the researchers hypothesize, even the enhanced flexibility may indicate a mellowing of the somatosensory system, calming paravertebral muscle spasms. It is fascinating to think about how joint mobility may connect with neuromuscular feedback and, ultimately, patient experience.

The methodology proposed here is not airtight. In particular, it begs the question about the correct way to establish a control group. Surely the patients in the control group knew they were receiving a sham treatment by simply laying on the table for a few seconds, casting into doubt the double-blind nature of this study. Many researchers are grappling with how to create a true placebo or control group to which an integrative intervention can be compared. This is especially challenging when the intervention is individualized, such as a unique homeopathic remedy or traditional Chinese medicine prescription. Perhaps a failsafe control group isn't absolutely necessary in all cases, but in this study patient perceptions may have played a significant role in the results seen and should have been better addressed.

Is spinal manipulation safe? We can't tell from this study, as it wasn't mentioned, but some reviews bring up that fact that the risks are non-negligible.[2,3] And in this case, the researchers cherry-picked a cohort of patients for whom there was likely very little risk involved (no disc herniations, no prior surgeries, etc.). How many of our patients with low back pain go through such an onerous screening process prior to receiving spinal manipulation, especially when they self-refer for such treatments? Very few to be sure. That said, when appropriately administered by trained professionals, spinal manipulation may be a reasonably safe choice for the "right" patient, but most experts in the literature are calling for more data to accurately depict the risk-benefit profile of spinal manipulation. ■

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COGNITIVE FUNCTION

ABSTRACT & COMMENTARY

Statin Use and Cognitive Effects: Not a Brain Drain

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

SYNOPSIS: Despite earlier concerns by the FDA about adverse effects of statins on cognitive functioning, a meta-analysis of data from more than 28,000 patients enrolled in 18 randomized, placebo-controlled trials of statin therapy failed to show a causal relationship between treatment and adverse neurocognitive effects for patients with and without cognitive impairment.

SOURCE: Ott BR, et al. Do statins impair cognition? A systemic review and meta-analysis of randomized controlled trials. *JGIM* 2015;30:348-358.

A consumer advisory issued by the FDA in February 2012 regarding potential adverse effects of statins on cognitive functioning concerned both physicians and patients, given the widespread use of statins for primary and secondary prevention of atherosclerotic cardiovascular disease, and hyperlipidemia treatment.[1] The postmarketing adverse reports, reported via the Adverse Event Reporting System, upon which the FDA based its warnings, generally described individuals older than 50 years age who experienced ill-defined memory loss, confusion, and foggy thinking with variable onset of symptoms ranging from 1 day to years after statin exposure. The statins involved were primarily the lipophilic statins simvastatin and atorvastatin (*see Table 1*). These symptoms resolved after discontinuation of the statins and in some instances recurred with resumption.

Ott and colleagues' meta-analysis and systematic review is timely and comprehensive in scope in its purpose to synthesize current evidence linking statin use with adverse cognitive outcomes. Since the public health implications of the FDA advisory were enormous, the authors compiled information on statin therapy and neurocognitive testing outcomes from all of the major randomized, placebo-controlled trials (RCTs) of statin therapy from several sources including Cochrane Central trial registries, MEDLINE, and EMBASE. Outcomes were analyzed separately in studies of both cognitively normal participants and in cognitively impaired trial patients with a diagnosis of Alzheimer's disease, and were designed to detect signals for adverse neurocognitive outcomes utilizing a summary statistic called the standardized mean difference (SMD).

Summary Point

- A large systematic review and meta-analysis of cognitive outcome data collected from the major randomized, placebo-controlled trials of statin treatment failed to show any association between statin therapy and cognitive decline in either cognitively intact or impaired patients with Alzheimer's disease.

SMDs are used in meta-analyses when the same outcome is being measured (neurocognitive outcomes in this case) using different psychometric scales. SMD values of ± 0.2 imply small differences, particularly when confidence intervals (CI) are narrow.[2]

For the 14 RCTs of cognitively normal patients included in the quantitative analysis, nine of the trials enrolled healthy patients without a specified medical diagnosis (age range 18 to 70 years), and five enrolled patients with cardiovascular risk factors (age range 40 to 83 years). Cognitive test outcomes among these participants at baseline included both global functioning and specific domains such as attention, executive function, memory, processing speed, and working memory.

For the four RCTs of cognitively impaired patients with Alzheimer's disease (mean age > 68 years), cognitive test outcomes were assessed with either the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-

Table 1: Statin Properties

Statin	Solubility	CYP P450 Metabolism	Drug Interactions	Blood Brain Barrier Permeability
Lovastatin	Lipophilic	Metabolized by 3A4 isoform	3A4 inhibitors: macrolides, calcium channel blockers, azole antifungals, grapefruit juice	Low
Simvastatin	Lipophilic	Metabolized by 3A4 isoform	3A4 inhibitors: macrolides, calcium channel blockers, azole antifungals, grapefruit juice	High
Atorvastatin	Lipophilic	Metabolized by 3A4 isoform	3A4 inhibitors: macrolides, calcium channel blockers, azole antifungals, grapefruit juice	Low
Fluvastatin	Lipophilic	Metabolized by 2C9 isoform	2C9 inhibitors: omeprazole, ritonavir, azole antifungals	High
Pravastatin	Hydrophilic	Minimal	2C9 inhibitors: omeprazole, ritonavir, azole antifungals	Low
Rosuvastatin	Hydrophilic	Minimal	2C9 inhibitors: omeprazole, ritonavir, azole antifungals	Low

Adapted from: Schachter M. Chemical, pharmacokinetic, and pharmacodynamics properties of statins: An update. *Fundam Clin Pharmacol* 2005;19:117-125; and Chong, PH, et al. Clinically relevant differences between the statins: Implications for therapeutic selection. *Am J Med 2001;111:390-400.*

Cog) or the Mini-Mental Status Examination. The ADAS-Cog measures language and memory and can determine incremental improvements or declines in cognitive functioning, which are important metrics in this group of patients.

This meta-analysis of the cognitive test data collected from these trials failed to show significant adverse effects of statins across all the measured cognitive domains in cognitively intact trial participants (SMD 0.01; 95% CI, -0.01 to 0.03; $P = 0.42$) or Alzheimer's disease trial participants (SMD -0.05; 95% CI -0.19 to 0.10, $P = 0.38$).

The authors also noted that adverse cognitive outcomes attributable to statins were rarely reported in trials involving cognitively normal or impaired subjects.

■ COMMENTARY

The time has now come to breathe a sigh of relief and reassure patients who require statin therapy that these medicines will not cause cognitive impairment.

This is an important message of reassurance because statins (HMG CoA reductase inhibitors) are the drugs of first choice for risk modification in patients at high risk for cardiovascular and cerebrovascular disease, the leading causes of death and disability (including cognitive disability) among adult patients. As a matter of fact, high levels of adherence and longer duration of statin therapy are associated with progressively increasing clinical benefits in terms of primary and secondary prevention of cardiovascular events.[3] The statin-associated relative risk reductions of 20-30% for myocardial infarction, 20% for ischemic stroke, and 10-15% for all-cause mortality underscore the importance of these medications.[4]

The multiple mechanisms of action by which statins mitigate risk include: 1) decreases in LDL cholesterol, 2) modification of inflammatory response, 3) antioxidant effects, 4) antithrombic effects, and 5) plaque stabilization effects such as reduction of smooth muscle proliferation and cholesterol accumulation.[5,6] See Table 1 for the most commonly used statins and differences in characteristics.

In 2013, a meta-analysis of eight randomized, controlled, statin-treatment trials showed no evidence of altered cognitive function between statin-treated and control patients.[7] A systematic review of three RCTs and 24 observational studies published in the same year showed that statin treatment was not associated with increased risk for incident dementia, Alzheimer's disease, or mild cognitive impairment. During the course of the study, Richardson et al reviewed the FDA postmarketing surveillance databases and found that the reporting rates for cognitive adverse events were similar for statins, losartan, and clopidogrel, although no studies suggested memory losses from the latter two commonly prescribed medications.[8]

Another important factor to consider about the FDA advisory was that the Adverse Event Reporting System reports that formed the basis of the warning did not mention concomitant medications taken by patients at the time of the adverse cognitive events. Several types

of medications may impair statin disposition and metabolism, especially for high-intensity therapy and for statins primarily metabolized by the P-450 cytochrome enzyme system (*see Table 1*). Simvastatin, in particular, as a cytochrome P-450 3A4 inhibitor, when taken in conjunction with macrolide antibiotics (3A4 inhibitors) or amiodarone (3A4 substrate and inhibitor), can result in both increased risk for QT prolongation and arrhythmias and statin-induced myopathy.

Although clinician and patient concerns about statins causing cognitive decline can largely be allayed as a result of this study, new onset of cognitive decline in a patient on statins for cardiovascular risk reduction deserves evaluation. It may be reasonable to discontinue certain other medications and screen for dementia, depression, as well as endocrine, infectious, inflammatory, vascular, and other degenerative illnesses, as root causes. It may be also reasonable to give a statin holiday. This presents an opportunity for a patient-centered discussion of options. ■

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CME QUESTIONS

1. **A recent study found that ginger root supplementation among non-insulin dependent diabetics may reduce hemoglobin A1c by approximately:**
   a. > 2.0
   b. 1.5
   c. 1.0
   d. < 1.0
   e. No reduction in hemoglobin A1c
2. **In individuals with small intestinal bacterial overgrowth (SIBO) as shown by a positive lactulose breath test, a 4-week treatment with herbal antimicrobial combinations:**
   a. was shown to be effective for the treatment of SIBO but not as effective as rifaximin.
   b. was shown to be as effective as rifaximin for the treatment of SIBO.
   c. was not effective for treatment of SIBO.
   d. was only effective for the treatment of SIBO after 4 weeks of treatment with rifaximin.
3. **In this study on men with low back pain, a high-velocity, low-amplitude spinal manipulation led to all of the following *except*:**
   a. less low back pain, as measured by a visual analog scale.
   b. a decrease in degrees of straight leg raise testing.
   c. greater spinal flexion (fingers closer to the floor on forward bending).
   d. increase in intervertebral disc space.
4. **Cognitive decline in a patient on statins should prompt which of the following?**
   a. Dementia screen
   b. Depression screen
   c. Evaluation for endocrine, infectious, and vascular inflammatory root causes
   d. Medication review
   e. All of the above

[IN FUTURE ISSUES]

- Acupuncture and Alzheimer's disease
- N-acetylcysteine for tobacco use disorder
- Metabolic syndrome and dietary fat
- Supplements and botanicals for diabetes