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Probiotics for the Treatment of Bacterial Vaginosis

By Donald Brown, ND

Naturopathic Physician and Director of Natural Product Research
Consultants, Seattle, WA.

Dr. Brown is a consultant to the supplement industry. He reports no relevant financial relationships to any of the probiotic strains discussed in this article.

BACTERIAL VAGINOSIS (BV) IS A COMMON VAGINAL INFECTION CAUSING significant gynecologic and obstetric morbidity. Though no single pathogen has been identified as the causative agent of BV, *Gardnerella vaginalis* and *Atopobium vaginae* are commonly associated with the condition.¹ Typical symptoms are said to include vaginal malodor, itching, dysuria, and thin discharge, but a substantial number of women with BV are asymptomatic.² BV has been associated with pelvic inflammatory disease, infections following gynecologic surgery, and preterm birth.³ Estimates suggest that 40% of cases of spontaneous preterm labor and preterm birth may be associated with BV.⁴ Some evidence also suggests the presence of BV may increase risk of HIV-infection.⁵

Treatment for the condition consists of metronidazole or clindamycin, administered orally or intravaginally. However, these antimicrobials are sometimes ineffective and many women have high recurrence rates following treatment (30% at 3 months and up to 50% at 6 months).⁶ A study of women with BV found that an adherent biofilm of primarily *G. vaginalis* and *A. vaginae* persisted 3 weeks after treatment with metronidazole.⁷

Vaginal Microbiota and BV

The estimated number of microbial species inhabiting the vagina is 50, compared to approximately 800 species in the intestinal tract.⁸ The vaginal microflora of healthy premenopausal women is generally dominated by *Lactobacillus* species, especially *Lactobacillus crispatus*, *L. gasseri*, *L. jensenii*, and *L. iners*.^{9,10} Factors influencing the vaginal microflora include hormonal changes (especially estrogen), vaginal pH and glycogen, and the use of topical microbicides.⁸ Lactobacilli in the vagina have been associated with the following protective roles against uropathogens (including those associated

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Summary Points

- Studies have shown that many strains of *Lactobacillus* may inhibit the growth of bacteria associated with bacterial vaginosis (BV).
- Antimicrobials can be ineffective against BV, and the recurrence rate is high following treatment.
- Adjunctive use of select probiotic therapies may improve treatment outcomes and recurrence rates with BV.

with BV): 1) inhibition of binding of pathogenic bacteria; 2) production of H₂O₂ and lactic acid that may limit pathogen growth; and 3) regulation of epithelial innate immunity.¹¹⁻¹⁴ A recent in vitro study found that *L. rhamnosus* RC-14 and *L. reuteri* RC-14 (see clinical research review below) are able to incorporate themselves into the biofilms created by *G. vaginalis* and *A. vaginae* and cause disruption of the biofilm and even some killing of the bacteria.¹⁵

The presence of H₂O₂-producing Lactobacilli spp. has been shown to be significantly higher in healthy women compared to those with BV.¹⁶ In one study, vaginal lactobacilli were isolated from 73.7% of 825 women without BV compared to 29.8% of 131 women with BV ($P < 0.001$).¹⁷ In a study of pregnant women, lactobacilli were isolated from 74.3% of women without BV compared to 38.4% of women with BV (odds ratio 0.7, 95%

confidence interval 0.6-0.8).¹⁸ In a study with Chinese women (aged 23-45 years), healthy subjects had a higher vaginal count of *L. crispatus* and a lower count of *L. iners* compared to women with BV.¹⁹ A study with pregnant Japanese women found that the presence of *L. crispatus*, *L. gasseri*, and *L. jensenii* was higher in healthy women compared to those with BV.²⁰ The study also found that presence of *L. iners* was associated with a greater risk of colonization by BV-related bacteria.

Probiotics for the Treatment of BV

Several clinical trials to date have been completed to study the effects of specific strains of lactobacilli to colonize the vaginas of women with symptomatic or asymptomatic BV, to reduce colonization of pathogens, and to improve symptoms and/or signs of BV when they are present. Although this review will focus primarily on more recent studies using probiotics as adjunctive therapy with standard antimicrobial therapy, readers also may want to review the excellent meta-analysis published in 2007 by Falagas et al that reviews the data from 10 studies published between 1992 and 2005.³

It is interesting to note that the more contemporary research using probiotics for the treatment of BV continues to be divided between intravaginal or oral application. The assumption for many years (and that continues in some circles) is that intravaginal application was the only means to efficiently deliver probiotics for the treatment and/or prevention of female genitourinary tract infections such as BV. Canadian researchers led by Gregor Reid have challenged this assumption with the development of two lactobacilli strains that were isolated from the vaginas of healthy women — *L. rhamnosus* RC-14 and *L. reuteri* RC-14 (previously identified as *L. fermentum* RC-14). Reid and colleagues found that oral administration of the two strains to 64 healthy women (ages 19-46 years) for 60 days resulted in a significant increase in vaginal lactobacilli at day 60 compared to a group taking placebo ($P = 0.05$), as well as a reduction in yeast and coliforms in the probiotic group.²¹ Although all women in the study reported being asymptomatic at the time of recruitment, 16 of 64 (25%) had asymptomatic BV at day 0. Of those subjects who did not have BV at baseline, 6 of 25 (24%) receiving placebo developed BV at day 35 and 6 at day 56 compared to none of the probiotic group ($P < 0.05$). A follow-up study found that oral delivery of the same strains was not only effective in colonizing the intestinal tract (based on fecal analysis) of healthy women but also the vagina.²²

Vaginal Application of Probiotics

In a single-center, randomized, observer-blinded study, 190 women (ages 18-45 years) diagnosed with BV were

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treated with clindamycin (300 mg bid) for 7 days and then randomized to receive a vaginal capsule containing *L. casei rhamnosus* (Lcr35 [Gynophilus; Laboratories Lyo-centre, France], 1×10^9 colony forming units [cfu]) or no further treatment the next 7 days.²³ Final vaginal swabs for Nugent scoring were taken 4 weeks after the last administration of clindamycin (the scoring system examines vaginal cells at random and applies a 0-3 score for normal [dominated by gram-positive bacilli resembling lactobacilli], 4-6 for intermediate [lactobacilli present along with gram-negative or gram-variable rods], and 7-10 for BV [no lactobacilli seen and cells colonized by gram-negative rods]). The primary outcome was the change in the Nugent score between baseline and at the end of the study of at least 5 grades.

At the end of the study, 83% of the women in probiotic group compared to 35% in the control group showed a reduction of the Nugent score by at least 5 grades ($P < 0.001$). A reduction of 8 grades on the Nugent score was found in 60% of women in the probiotic group compared to 14% in the placebo group. The median difference between initial and final swabs was 6.61 in the probiotic group and 4.13 in the control group ($P < 0.001$). There is no indication that adverse events were tracked during the study. The results suggest that intravaginal application of Lcr35 following antibiotic therapy is able to effectively restore the vaginal flora to a healthier level based on the Nugent score.

In a randomized, double-blind, placebo-controlled trial (RDBPCT), 100 women (mean age 34 years) with BV were treated with 2% clindamycin cream for 7 days and then randomized to receive vaginally inserted capsules containing either a placebo or a probiotic combination of *L. gasseri* (Lba EB01-DSM 14869) and *L. rhamnosus* (Lbp EB01-DSM 14870) containing $1 \times 10^{8-9}$ cfu of each organism per capsule.²⁴ The two strains were cultured from healthy women in Norway. Following the 7-day course of clindamycin, patients were instructed to insert the vaginal capsules daily for 10 days or until menstruation started. After each menstruation, this 10-day application was repeated for 3 cycles. Women who were considered to still have BV after the first menstruation were retreated with clindamycin and excluded from the study. Treatment was considered a cure when the Hay/Ison score was 1; a score of 2 was designated as “improved,” and a score of 3 was a treatment failure (the Hay/Ison criteria uses the following grades based on a gram-stained vaginal smear: Grade 1 [normal] — lactobacilli morphotypes predominate; Grade 2 [intermediate] — mixed flora with some lactobacilli present but Gardnerella and/or Mobiluncus morphotypes also present; and Grade 3 [BV] — predominately Gardnerella and/or Mobiluncus morphotypes and few or absent lactobacilli). Treatment efficacy was based on both cure after one month and the length of time to relapse us-

ing the Kaplan-Meier survival analysis.

The initial intention to treat (ITT) cure rate after the first menstruation was 64% for the probiotic group and 74% for the placebo group. However, when considering missing or unclassified vaginal swabs or missed capsules, the rates were 77% and 78%, respectively. The 76 women initially classified as cured were followed until their sixth menstrual cycle or until relapse. There was a significant difference ($P = 0.027$) in favor of the probiotic-treated women in duration of time from cure to relapse. At the end of the study, 64.9% of the probiotic group compared to 46.2% of the placebo group were cured ($P = 0.042$). Adverse events were similar in both groups and there was one possible case of vaginal discomfort due to allergy in the probiotic group.

Oral Use of Probiotics

In a RDBPCT, the efficacy of an oral probiotic combination was studied in women being treated for BV with metronidazole.²⁵ One hundred and twenty-five women (18-44 years old) initially were entered in the study. All subjects received oral metronidazole (550 mg bid) from days 1 to 7 and were randomized to receive one capsule containing *L. rhamnosus* GR-1 (1×10^9 cfu) and *L. reuteri* RC-14 (1×10^9 cfu) or placebo orally bid from days 1 to 30. Chris Hansen, Horsholm, Denmark, supplied the probiotic combination. The primary outcome was the cure of BV as determined by a normal Nugent score, absence of clue cells, negative sialidase test, and no signs or symptoms (no discharge or fishy odor) of BV at day 30.

One hundred six women returned for the 30-day follow-up visit. In the probiotic group, 88% of women were cured compared to 40% in the antibiotic/placebo group ($P < 0.001$). Of the remaining probiotic subjects (12%), none had frank BV. All had mild irritative symptoms, no discharge or odor, a weakly positive sialidase score, and intermediate Nugent score. This contrasted with the remaining 34 placebo subjects, of which half had BV and the other half had an intermediate status. According to the study report, 100% of the probiotic-treated patients no longer were diagnosed with BV, while 30% of the placebo group was positive. High counts of *Lactobacillus* sp. ($> 10^5$ cfu/ml) were recovered from the vagina of 96% of the probiotic-treated subjects compared to 53% of controls at day 30. No significant adverse events were reported. The study reports a high dropout rate in the probiotic group ($n = 16$) compared to the placebo group ($n = 3$). Although the investigators suggest this is due to the patients feeling better and assuming they were cured, an intention-to-treat analysis that included these subjects should have been included.

A second RDBPCT studied the same oral probiotic combination in 64 women (ages 16-51 years) diagnosed

with BV.²⁶ All patients were treated with a single dose of tinidazole (2 g) and then randomized to receive two capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (each capsule contained 1 x 10⁹ cfu of each probiotic strain) or placebo orally in the morning for 28 days. Subjects, who reported suffering from recurrent BV, were distributed in a balanced fashion between the probiotic (n = 8) and placebo (n = 7) groups.

At day 28, significantly more women in the probiotic group than the placebo group had normal vaginal smears according to the Nugent score ($P = 0.011$) and Amsel criteria ($P = 0.001$; the Amsel criteria are used in clinical practice to diagnose BV and include: 1) thin, white, yellow, homogenous discharge; 2) clue cells on microscopy; 3) pH of vaginal fluid of > 4.5; and 4) release of a fishy odor on adding 10% potassium hydroxide). This translated to a cure rate of 87.5% for the probiotic group compared to 50% for the placebo group ($P < 0.05$). The vaginal smears of the placebo group showed a higher presence of gram-variable cocci-rods and curved gram-negative rods deemed indicative of BV compared to the probiotic group ($P < 0.05$). Considering only those patients with recurrent BV, 75% of those in the probiotic group were cured compared to 57.1% in the placebo group ($P < 0.05$). No significant adverse events were reported.

Conclusion

The role of “bacillus” in the health of the female genitourinary tract was first described in 1892 by Albert Döderlein. Long referred to as “Döderlein bacillus,” we now know that the healthy vaginal flora is made up primarily of members of the *Lactobacillus* family. Various in vitro studies have demonstrated the ability of specific strains of lactobacilli to inhibit the growth of bacteria causing BV as well as inhibiting adherence and possibly interfering with the formation of biofilms.

Newer clinical studies suggest that the adjunctive use of probiotics with standard antimicrobial therapy may not only improve treatment outcomes but also prevent recurrence in women with BV. While promising, the data are split between different routes of probiotic administration as well as varied proprietary strains. With two studies confirming efficacy, the oral combination of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 appears to be the frontrunner for future clinical studies (2 x 10¹⁰ cfu of each strain per day). Larger and longer trials with a focus on prevention are needed in a more diverse group of women to firmly establish probiotics as a viable clinical option for the treatment and prevention of BV. Considering the fact that women with BV have been treated with the same antimicrobial treatments for the past 40 years and the significant rate of recurrence paired with the health risks associated with BV, the further development of probiotics in the management

and prevention of BV appears to be a sound investment.

Recommendation

Women being treated for BV with antimicrobial therapy should be educated about the potential benefits of adjunctive use of specific probiotic strains to potentially improve treatment outcomes, prevent recurrence, and re-establish healthy vaginal flora. Preliminary data suggests that longer-term ingestion may be more effective than short-term ingestion and may point to the need for women with a history of recurrence to consider ongoing use of probiotics. ■

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Probiotics for Diarrhea or Eczema: Updates

By David Kiefer, MD

Clinical Instructor, Family Medicine, University of Washington, Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tucson; Adjunct Faculty, Bastyr University, Seattle

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

Introduction

EVIDENCE FOR THE USE OF PROBIOTICS IN A VARIETY OF medical conditions continues to accumulate. Defined as live, nonpathogenic microorganisms that benefit the host (humans, in this case) when provided in adequate amounts,¹⁻³ probiotics comprise a variety of species of bacteria and one yeast, and are found in mixed or single species preparations, recommended in a variety of dosages. This review will update two prior issues of *Alternative Medicine Alert* that addressed probiotic therapy,^{4,5} focusing on the use of probiotics in gastrointestinal and atopic disease. The previous article in this issue reviews data regarding the use of probiotics in gynecologic conditions.

Physiology

Both in vitro and in vivo research have demonstrated that probiotic species outcompete pathogenic bacteria for binding sites in the gastrointestinal tract and help to strengthen the gastrointestinal epithelial barrier.¹⁻³ Probiotics also, predictably, modify the gastrointestinal flora, and can lead to systemic and local changes in immune system function.^{1,2} Relevant to childhood atopy, probiotics may help temper excessive immune system and inflammatory responses to foreign antigens through changes in various cytokines, decrease exposure to dietary antigens by gastrointestinal macromolecule alterations, and improve serum immunoglobulin A responses.^{2,6,7}

Probiotic species with known beneficial physiological effects include numerous species of *Lactobacillus* (acidophilus, rhamnosus, bulgaricus, reuteri, and casei), *Bifidobacterium* species, *Streptococcus* species, *Enterococcus faecium*, and the yeast, *Saccharomyces boulardii*.^{2,8}

Clinical Trials

Diarrhea. There are numerous clinical studies describing the effects of probiotics on the prevention or treatment

Summary Points

- Probiotics can be defined as live, nonpathogenic microorganisms that benefit the host when provided in adequate amounts.
- Specific probiotic therapy may reduce inflammatory changes in response to antigenic exposure.
- Probiotic therapy may prevent antibiotic-associated diarrheal illness, as well as help prevent and treat viral diarrheal disease; however, probiotics appear less beneficial in the setting of traveler's diarrhea.
- Atopic dermatitis in newborns may be prevented by the administration of probiotics during the late third trimester, breastfeeding, and to the infant during the first year of life.
- Probiotic therapy appears to be generally safe, but care must be taken in certain situations, notably immunosuppression.

diarrhea of varying etiologies and in different demographics. Of note, due to variations in study design, probiotics strains used, doses administered, and formulation, the results of the different studies are difficult to compare. Nonetheless, one meta-analysis of 34 studies found that probiotics significantly reduced the risk of acute diarrhea of diverse causes by 34% (confidence interval [CI] 8-53%, $P = 0.013$).⁹ The effect was similar across probiotic species, including *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, and *S. boulardii*, though the overall effect seemed to be higher in children than for adults. Another systematic review of probiotics for the prevention of childhood diarrhea supported a positive preventive effect, primarily in the dose range of 5-40 billion colony forming units (cfu) daily of either *L. rhamnosus* or *S. boulardii*.¹⁰

In addition to this preventive role, probiotics may function in the treatment of acute infectious diarrhea in both children and adults. A systematic review found that the duration of symptoms may be shortened by about 30 hours when using probiotics for acute diarrhea.¹¹ An example of a specific intervention examined in this context is a three times daily dosage of 1 billion cfu of *E. faecium* for adults with acute diarrhea.¹² In addition, clinical trials have shown that different probiotic strains, including *Lactobacillus* species (*reuteri*, *rhamnosus*, or *casei*) and *S. boulardii* are useful in reducing the severity and duration of acute infectious diarrhea in children; the oral administration of probiotics shortens the duration of acute diarrheal illness in children by approximately 1 day.¹³ The evidence from studies on viral gastroenteritis (e.g., rotavi-

rus) is more convincing than the evidence for bacterial or parasitic infections.¹³

The coadministration of some probiotic strains may prevent antibiotic-associated diarrhea (AAD).¹⁴ The same meta-analysis that addressed children's infectious diarrhea found that children receiving *Lactobacillus* species, *Streptococcus* species, or *S. boulardii* plus antibiotics had a 30% reduced incidence of AAD when compared to placebo groups.¹³ In adults, *Lactobacillus* species and *S. boulardii* seem to significantly reduce the incidence of AAD.¹⁵ Both of these reviews were corroborated by a meta-analysis finding a 52% reduction of AAD in both children and adults taking probiotics (CI 35-65%, $P < 0.001$).⁹

For other types of diarrhea, there is less research. A meta-analysis of clinical trials for probiotics in traveler's diarrhea showed that *S. boulardii* and a mixture of *L. acidophilus* and *Bifidobacterium bifidum* prevented traveler's diarrhea, but there was a large variation in methodology between the trials, making it difficult to draw firm conclusions.¹⁶ Another meta-analysis failed to find benefits for probiotics in the prevention of traveler's diarrhea.⁹ Interestingly, probiotics may be useful in the treatment of stress-induced diarrhea,¹⁷ as well as the prevention of diarrhea from *Clostridium difficile* after antibiotic treatment.¹⁸

Atopic Dermatitis. Prior issues of *Alternative Medicine Alert*^{1,2} detailed clinical trials and conclusions based on the probiotic-eczema medical literature through 2008. At that time, the primary conclusions were that probiotic supplementation in pregnant or breastfeeding women, or for their newborn helps to decrease the incidence and severity of newborn atopic dermatitis, especially if there is a history of atopy in the family.^{19,20} Common dosing in this context was 5-10 billion cfu, using a variety of single or multiple probiotic species.

Since that time, further clarification about the use of probiotics to prevent or treat atopic disease, either in the perinatal period or after delivery, has surfaced in clinical trials. One recent randomized clinical trial replicated the common methodology for a probiotic intervention for atopy, namely that pregnant women with a family history of atopic disease ($n = 112$) were randomized to receive probiotics (a blend of species, 4.8 billion cfu daily) from 2 months before delivery to 3 months afterward.²¹ The prevalence of eczema in the newborn was found to be less in the probiotic group vs placebo at 1 year of age (18.2% vs 40.0%, $P = 0.048$). This positive effect has not always been replicated in clinical trials, prompting researchers to search for reasons to explain the disparities. For example, it is possible, though not definitively proven, that probiotic supplementation more adequately prevents atopic dermatitis in children who are IgE sensitized, that is, those

children who have a positive skin prick test and/or elevated serum IgE levels.²² This conclusion would dovetail with in vitro research documenting cytokine and immune system effects.

With respect to treatment of childhood eczema, a recent meta-analysis of 12 clinical trials did not find any probiotic benefit on symptoms or investigator rating of eczema severity.²³ There was, as with other reviews of this topic, a significant heterogeneity of study quality and methodology (including dosing, from 1-100 billion cfu daily, and probiotic species used) that could compromise the final conclusion. Lacking in this review article, and, in fact, the other reviews also mentioned in this article, is a subgroup analysis by dose or species that would help to statistically clarify the relationship of these two important variables to clinical outcome.

Other Conditions

Advances in clinical research have shown, to varying extents, effects of probiotics on numerous different clinical conditions (*see Table*). It is beyond the scope of this article to fully review the relevant literature but researchers have found some evidence that probiotics may maintain remission from pouchitis in inflammatory bowel disease,²⁴ induce remission in Crohn's disease,²⁵ help relieve symptoms of allergic rhinitis or asthma,²² and help to prevent the development of acute upper respiratory tract infections from infancy onward.^{26,27} In addition, probiotic supplementation may improve some, but not all, of the symptoms associated with irritable bowel syndrome.²⁸⁻²⁹ Not all clinical trials have found benefit; probiotic supplementation for childhood constipation has had mixed results^{1,30,31} and probiotics do not seem to decrease colonization with vancomycin-resistant *E. faecium* (a variety

of the same species that is part of our normal flora and a constituent of some probiotic supplements) nor help clinical or laboratory findings in hepatic encephalopathy.¹

Dosing

It is not possible to suggest a general dosage for probiotics. The dose needed depends greatly on the species, product, and indication. Most of the products employed in research trials contain between 100 million and 10 billion cfu/dose, and used up to 20 billion cfu daily, though higher doses are sometimes recommended for acute indications.² As a general rule, extrapolating from clinical trials, dosing on the higher end of the dose range (5 billion cfu daily for children and 10 billion cfu daily for adults) would be more likely to yield a positive clinical effect for prevention or treatment of gastrointestinal conditions or atopic dermatitis.^{2,4}

Adverse Effects

Probiotics are considered safe, with a low risk of adverse effects, in healthy individuals.⁷ Some clinical trials have documented a range of adverse effects, though often similar in incidence to side effects documented in members of placebo groups.²³ Mild adverse effects in children may include rash, nausea, gas, flatulence, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and poor appetite, with no serious adverse effects in otherwise healthy children.^{10,32} In other populations, self-limiting and mild gastrointestinal discomfort or flatulence have been reported.²

There have been case reports of bowel ischemia and sepsis in children, for which some authors believe that probiotics should be relatively contraindicated in certain populations, such as preterm infants, children with short-gut syndrome, immunocompromised children and adults, or in people with "chronic disease," the latter presumably due to decreased immune system function.^{2,22,23,32}

Conclusion

Probiotics comprise a range of species, including bacteria such as *Lactobacillus* and *Bifidobacterium* species, and the yeast *S. boulardii*. The physiological effects of orally administered probiotics, as demonstrated in both in vitro and in vivo research, comprise not only local gastrointestinal effects, such as displacement of pathogenic bacteria and improvement of inter-intestinal cell tight junctions, but systemic improvements in cytokine profiles and immune system function. Clinical trials exist that have explored the use of probiotics for numerous conditions, including diarrhea and atopic dermatitis. The data are convincing for the use of probiotics to prevent both acute infectious diarrhea and antibiotic-associated diarrhea, as well as to treat viral gastroenteritis, helping

Table: Clinical conditions beyond diarrhea and atopy for which there is some evidence for the use of probiotics¹

Cancer prevention (in vitro)
Hyperlipidemia
Maintaining remission of ulcerative colitis or Crohn's disease
Oral health (i.e., prevention of dental caries)
Obesity/overweight children and adults
Ventilator-associated pneumonia
Pre-term neonates: necrotizing enterocolitis and all-cause mortality

children (more than adults) to recover approximately one day faster, when used in an average dose of 10 billion cfu daily (5 billion cfu for children). Probiotics seem less likely to help prevent traveler's diarrhea. For atopic dermatitis, there is little doubt that probiotics, begun during pregnancy and continued through the first year of life, help to decrease the prevalence and severity of eczema in newborns born into so-called "atopic families." It is possible that positive probiotic effects are more likely to occur in newborns who are IgE sensitized, but this needs to be further clarified with more clinical trials. The medical literature is mixed on whether probiotics are a useful adjunct in the treatment of already-existing eczema. Adverse effects of probiotics are generally rare and mild, though caution is warranted in select individuals, such as those who are immunocompromised.

Recommendation

Probiotics composed of a mixture of species and dosed at a minimum of 5 billion cfu daily for children and 10 billion cfu daily for adults should be given to anyone on antibiotics, except in the context of severe illness or chronic disease, or in preterm infants, infants with short-gut syndrome, or anyone with a compromised immune system. In addition, children who are at risk of acute diarrheal illness, such as those who attend day care, should ingest daily probiotics, either from food or supplements. Finally, in families with a high prevalence of atopic disease, probiotic supplementation should be considered for inclusion as a part of a pregnant woman's regimen and continued through the early months of a healthy newborn's life, in order to help prevent the development of atopic dermatitis. Convincing clinical trials and physiologic mechanistic work show that probiotic therapy is a generally safe and important therapeutic tool for enhancing gastrointestinal and immune system function. ■

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Yay Yoga! More Evidence for Helping Low Back Pain

ABSTRACT & COMMENTARY

By Nancy Selfridge, MD

Associate Professor, Department of Integrated Medical Education, Ross University School of Medicine, Commonwealth of Dominica, West Indies

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

Synopsis: Yoga, a stretching program, and a self-care book on low back pain were compared in a three-armed randomized trial for patients with chronic low back pain. The findings showed that yoga was significantly more effective than was using the self-care book, whereas yoga and stretching classes were equally effective. The benefits lasted for at least 26 weeks.

Source: Sherman K, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. *Arch Intern Med* 2011;171:2019-2026.

THE COSTS OF CHRONIC LOW BACK PAIN IN TERMS OF HUMAN suffering, disability, and economic impact are inarguably large. Long-term evidence of efficacy and safety for analgesic use is still lacking, and although there is some evidence to support the recommendation of non-drug treatments — such as acupuncture, chiropractic, and massage — none have been proven to be highly effective.¹ A number of studies have shown that yoga may be an effective treatment for chronic or recurrent low back pain. A recent meta-analysis of controlled studies concluded that yoga is a useful approach with moderate effect sizes on pain and associated disability.² In this new study of yoga for low back pain, using a larger sample size, the authors set out to confirm previous findings that yoga is helpful for reducing pain and increasing function for patients with low back pain. Because yoga training includes a mental component in addition to the physical stretching and strengthening, the authors also designed the study to determine if yoga was superior to a stretching only program.

Methods

Patients with low back pain were recruited primarily from a large western Washington health care organization and augmented with outreach to the general population. Exclusion criteria included back pain due to structural or underlying medical conditions, a history of previous back surgery, a history of litigation, pain less than 3 months' duration, or minimal pain at the time of screening. Participants also had to be able to attend classes and had to express willingness to do home practice. A total of 228 participants were randomized to three treatment arms in a 2:2:1 distribution: yoga, stretching, and self-care. The study staff was blinded to treatment assignments. The yoga and stretching classes consisted of 12 standardized weekly 75-minute classes. Adherence to treatment protocols was monitored. Participants in both classes were asked to practice for 20 minutes on non-class days and were given written and video practice guides to assist them. A third cohort of participants received a self-care book detailing causes of low back pain and advice on exercising, lifestyle modifications, and managing flares of pain.

Telephone interviewers collected study data at baseline and at 6, 12, and 24 weeks. Primary outcomes were scores on self-rated symptom "bothersomeness" (0-10 scale) and scores on the Roland Morris Disability Questionnaire (RDQ), a widely used, validated instrument for measuring health status in low back pain patients. Secondary outcomes included activity restriction, global rating of improvement, and patient satisfaction. Participants also were asked about adverse events. Primary and secondary outcomes were analyzed using regressions and generalized estimating equations. All analyses were subjected to intent-to-treat principles.

Summary Points

- Therapeutic yoga has the potential to offer not only physical conditioning, stretching, and strengthening, but also a component of mental relaxation.
- In this study, yoga therapy was equally effective in relieving chronic low back pain as a standardized regimen of stretching exercises, and more effective than self-care.

Results

Adherence in the yoga and stretching cohorts was similar: The proportion of participants attending at least eight classes was 65% for yoga and 59% for stretching. Home practice times were similar in both of these active groups for the duration of the study. Of the self-care participants, 86% reported reading at least some of the book. Connection with class instructor was rated similarly in the yoga and stretching groups, as was support from classmates.

RDQ scores showed superior function in the yoga group compared with self-care at 12 weeks (95% confidence interval [CI], -3.7 to -1.3) and 26 weeks (95% CI, -3.1 to -0.5). The stretching group also demonstrated superior function compared to self-care at 6 weeks (95% CI, -3.0 to -0.4), 12 weeks (95% CI, -3.4 to -1.0), and 26 weeks (95% CI, -2.8 to -0.2). Adjusted Relative Risk (RR-95% CI) for pairwise comparisons of RDQ scores of at least 50% improvement at 26 weeks was 1.90 for yoga vs self care; 1.63 for stretching vs self care; and 1.17 for yoga vs stretching. Differences in outcomes between the yoga and stretching groups were not statistically significant. The only meaningful differences between groups for symptom “bothersomeness” occurred at 12 weeks wherein the yoga group was significantly less bothered by symptoms than the self-care group (95% CI, -1.74 to -0.41). Thirteen participants in the yoga group and 13 in the stretching group reported mild-to-moderate adverse experiences, mostly increased back pain. Only one self-care participant reported increased pain after doing recommended exercises. However, compared to self-care, yoga and stretching participants reported higher satisfaction with care and were more likely to rate their back pain as better, much better, or completely resolved at all follow-up intervals.

The authors concluded from this study that yoga is an effective intervention for improving symptoms and disability due to chronic low back pain and that the effect is most likely due to the physical components of a yoga practice, since stretching appears to offer similar benefits.

■ COMMENTARY

This study supports a growing body of research that suggests that yoga is a viable and effective treatment option for patients with chronic low back pain. The sample size for this study was about twice that of those in previous published clinical trials, a frequent criticism of the prior research. Another strength of this study is that the authors attempted to separate the physical and mental effects of yoga on back pain with the use of the stretching class treatment group, working under the assumption that yoga might have therapeutic effect due to the breathing and mental training that is part of traditional yoga practice, and is not a part of conventional stretching classes. The yoga method used in this study was a viniyoga style that is therapeutically oriented. The yoga instructors were comfortable with modifying postures for persons with physical limitations. Simply suggesting a yoga class to chronic low back pain patients without considering the style and instructor orientation appears to be unwise because of the wide variation in styles, levels of difficulty, and instructor training and experience in yoga classes available at large.

Further, the various styles of yoga for low back pain have not been compared for efficacy and safety. An additional drawback is that classes can be expensive, though DVDs and online instruction offer low-cost alternatives. Unsupervised instruction may be fraught with hazards, and there is a beneficial effect from the social support that prevails in a class format, which remains challenging to measure. Though yoga and stretching exercises seem similarly effective in this study, most stretching exercise classes available in community settings are not of 75 minutes duration. Comparing yoga to a more typical stretching class of 30-45 minutes would yield valuable information and thus should be considered as a future study. Adherence to any physically active intervention for chronic pain remains problematic even in the present study, where the adherence rate is similar to past studies on exercise for back pain.

Thus, recommendations of yoga for back pain patients must take into consideration the patients' willingness to pursue a physically active course of treatment that requires at least some motivation and self-efficacy. Fear of movement and exercise in patients with chronic low back pain may be an obstacle to overcome for them to benefit from yoga and stretching, both of which were shown to be effective in this study. ■

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Massage — With Your Genes On

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: Through a small but exquisite study, the authors of this investigatory intervention trial provide a plausible subcellular explanation for massage therapy's purported benefits on injured muscle using muscle biopsy and subsequent gene profiling. The application of similar study techniques might be expected in future studies of other CAM therapies directed against pain.

Source: Crane JD, et al. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. *Sci Trans Med* 2012;119:1.

THE AIM OF THIS STUDY WAS TO ASSESS THE INFLUENCE OF massage therapy within muscle that had completed a bout of intense exercise. Eleven recreationally active (and brave!) male volunteers participated in the study. After an overnight fast, subjects reported to the laboratory on two separate occasions, 14 days apart. They were permitted to follow their normal diets up until fasting, but were asked to abstain from moderate to intense physical exertion for 72 hours prior, alcohol consumption for 48 hours, and caffeine ingestion for the previous 12 hours. A 355-kcal defined formula diet was ingested 2 hours before each study session.

At the beginning of the first visit, a baseline muscle biopsy was taken from the quadriceps muscle of a randomly assigned leg to serve as the resting control sample. After the biopsy, each subject underwent testing for peak aerobic capacity (VO_{2peak}) on an upright bicycle ergometer.

At the second visit, subjects performed a bout of exhaustive aerobic exercise followed by randomized massage therapy. The exercise activity again consisted of upright cycling and was performed as follows: 1) pedaling at a workload calculated to elicit 60% of each subject's predetermined VO_{2peak} for 30 minutes at 70-90 rpm, followed by 2) an increase in exercise intensity to a workload equivalent to 65% VO_{2peak} for 5 minutes, then 3) back down to 60% for 5 minutes, and 4) increased to 70% VO_{2peak} for 5 minutes, then 5) dropped to 60% for 5 minutes, and 6) so on until a maximum of 85% VO_{2peak}

Summary Points

- Based on the findings of this study, massage therapy appears to modulate pro-inflammatory cytokines, increase mitochondrial production, and enhance protein synthesis in exercised muscle tissue.
- Massage therapy works similar to NSAIDs in mildly damaged muscle tissue, but is safer and more pleasant.

was achieved. Exercise was continued until participants reached exhaustion, defined as the inability to maintain a cycling cadence above 70 rpm.

Subjects were allowed to recover for 10 minutes while massage oil was lightly applied to both quadriceps. One leg was then selected at random to receive 10 minutes of massage from a registered massage therapist. Repeat quadriceps muscle biopsies were obtained immediately after massage therapy, and then after 2.5 hours of additional recovery time.

Whole-genome, untargeted microarrays were performed initially to screen for expressed genes induced by massage; five were identified that were differentially expressed in the muscle immediately after massage, and four genes that were differentially expressed 2.5 hours after treatment. Real-time reverse transcription-polymerase chain reaction (RT-PCR), protein signaling analysis, and metabolite quantification were performed to characterize processes occurring within the muscle in association with massage.

The authors describe a pathway starting with myofibrillar damage as a result of exercise-induced muscle contractions or direct trauma, and ending with localized inflammation and resultant pain; in between there lies a complex interplay of mechanotransduction, cell signaling, activation and suppression of regulatory proteins, immune cell recruitment, and alterations in glucose uptake. The authors do a terrific job of describing this in a detailed yet accessible manner. The bottom line results emphasize the sub-cellular and molecular levels: massage therapy appears to 1) drive processes that modulate inflammation, in part by reducing the synthesis of pro-inflammatory cytokines (which may interfere with muscle repair), and 2) promote repair of damaged muscle tissue by improving contractile function, enhancing glucose uptake, reducing intracellular stress, promoting protein synthesis, and increasing the production of mitochondria. The temporal nature of the findings suggest that processes related to cytoskeletal integrity take place early following massage therapy, while those impacting inflammation occur later. Of note, no changes in glycogen fractions and muscle lactate levels were identified.

The authors close by stating that massage therapy may work in ways similar to NSAIDs, yet be safer, and potentially more effective in addressing muscle injury, especially to areas of known low blood flow such as the muscle-tendon interface. The mechanisms by which massage therapy provides therapeutic benefits include increased mitochondrial production, enhanced protein synthesis, and modulation of pro-inflammatory cytokines.

■ COMMENTARY

Everyone knows that massage therapy feels good, and numerous studies show that massage can contribute to recovery from a variety of painful conditions, but only rarely are subjective outcomes sufficient to carry the day when it comes to determining precise clinical indications, or helping patients to secure insurance reimbursement for treatment. It has long been presumed that massage therapy helps relieve aching, overworked, and damaged muscles through a combination of actions that promote increased blood flow and clearance of lactic acid buildup, among others, but in truth there has been relatively little mechanistic research performed that focuses on how massage therapy, and other CAM interventions, might provide relief. And then this paper was published.

Creating a biological understanding of therapeutic impact related to any therapy is imperative. Scientific inquiry into CAM treatments that takes advantage of technological advances in molecular biology and genetics is rare. There are reasons, of course, but the fact remains. The results of this study show it can, and should, be done more frequently.

The researchers confirmed first that damage had been done to cells of the quadriceps muscle through toluidine blue staining. On a molecular level, they then showed that a mere 10 minutes of massage therapy created changes that decrease inflammation, hasten muscle repair, decrease pain, and promote recovery. Some of these actions are unique, some are similar to those associated with the use of anti-inflammatory medication, but few would argue with the idea that massage therapy is infinitely more enjoyable than popping pills, and significantly safer.

Kudos to the researchers (and the courage and vitality of the volunteers) for a study that not only offers answers that may pave the way for greater advantage for patients, but also lights the path for more in-depth biological evaluation of additional therapies, both conventional and alternative in nature. ■

CME Objectives

After completing the program, physicians will be able to:

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

CME Questions

- The presence of hydrogen peroxide-producing lactobacilli species in the vagina has been shown to be significantly higher in healthy women compared to those with bacterial vaginosis. Lactobacilli in the vagina have been associated with which of the following?**
 - Inhibition of binding of pathogenic organisms
 - Production of hydrogen peroxide and lactic acid
 - Regulation of epithelial innate immunity
 - All of the above
- Which of the following strains has been shown to be potentially efficacious for bacterial vaginosis when used orally?**
 - Lactobacillus rhamnosus* Lcr35
 - L. rhamnosus* GR-1 and *L. reuteri* RC-14
 - L. acidophilus* 2012
 - L. gasseri* (Lba EB01-DSM 14869) and *L. rhamnosus* (Lbp EB01-DSM 14870)
- Which type of diarrhea has the least evidence of benefit from probiotic supplementation?**
 - Traveler's
 - Antibiotic-associated
 - Treatment of acute infectious diarrhea
 - Prevention of acute infectious diarrhea
- Which of the following genera (assume a variety of species) of probiotic microorganism have been studied in clinical trials and seem to have some proven effect on either gastrointestinal or atopic disease, or both?**
 - Lactobacillus*
 - Bifidobacterium*
 - Streptococcus*
 - All of the above
- Which of the following is true about yoga for back pain?**
 - Meta-analyses suggest dubious benefit for pain and disability.
 - Styles of yoga have been compared and viniyoga has greater efficacy.
 - Adherence to yoga programs for back pain is superior to other exercise programs.
 - Standardized programs of yoga and stretching appear to be equally beneficial.