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Lipids, Inflammation, and CAD: The View from JUPITER

ABSTRACT & COMMENTARY

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Synopsis: *Healthy middle-aged men and women with normal LDL-cholesterol levels and elevated levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) show significant decreases in clinical cardiovascular events when treated with rosuvastatin vs placebo. The identification and management of chronic systemic inflammation has a significant impact on the treatment of cardiovascular diseases particularly for persons who don't have other risk factors that would target them for primary prevention.*

Source: Ridker PM, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-2207.

In the justification for the use of statins in prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, a large multicenter randomized, double-blind, placebo-controlled trial of 17,802 healthy middle-aged subjects, Ridker et al have definitively shown that an intervention to decrease levels of the inflammatory biomarker hsCRP resulted in decreased incidence of the clinical endpoints of myocardial infarction, stroke, and combined cardiovascular (CV) death.[1] This study is particularly noteworthy because the patients had median levels of LDL-cholesterol of 108 mg/dL, which is below the currently established threshold of treatment recommended by the National Cholesterol Education Project Adult Treatment Panel III 2004 guidelines.[2] This is also the first large-scale primary prevention trial that included a substantial proportion of female and minority subjects (approximately 38% and 19%, respectively, for both placebo and rosuvastatin-treated groups).

The study was terminated after a median follow-up of only 1.9 years, at which time the data safety and monitoring board found

statistically significant improvements in clinical outcomes for patients treated with the statin drug, rosuvastatin. At the time of the study termination, the median LDL-cholesterol level was 55 mg/dL (down from a baseline median level of 108 mg/dL) and the median hsCRP level was 2.2 mg/L (down from a baseline median hsCRP of 4.2 mg/L) with a hazard ratio of 0.53 for rosuvastatin for the clinical endpoints of myocardial infarction, stroke, or confirmed CV cause of death. The clinical benefits were observed in every subgroup. Interestingly, subjects whose only risk factors were age and hsCRP elevation benefited from rosuvastatin as much as higher-risk subjects.

■ COMMENTARY

Since 20% of all coronary events occur in individuals without any of the major Framingham risk factors and sudden cardiac death accounts for 50% of all CHD deaths,[3,4] this study is pivotal in that it provides a way for primary care physicians to correctly identify these individuals for preventive treatment. Given that CV disease and atherothrombosis have inflammation as a root causative factor, the JUPITER trial raises another formidable question: Can inhibition of inflammation by agents other than statins reduce the rates of cardiovascular events? As a matter of fact, there is evidence from several clinical studies that two interventions can reduce inflammatory markers as well as clinical CV endpoints.

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The first intervention is a dietary modification to increase intake of the omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as fish meals or supplements and the second is a lifestyle intervention to treat periodontal disease with professional dental care and prevent it by proactive early attention to the daily oral hygiene practices of tooth brushing and flossing.

An important implication of these interventions is that, although they will never make huge profits for large pharmaceuticals, they have the potential to improve the overall health and quality of life of individual patients in that each has ancillary benefits such as decreased tooth and alveolar bone loss (periodontitis treatment and prevention), increased fertility (omega-3 fatty acids),[5] lowered blood triglyceride concentrations (omega-3 fatty acids),[6] and improved glycemic control (periodontal disease treatment).[7]

Omega-3 Polyunsaturated Fatty Acids

The necessity of the dietary intervention comes as no surprise because the dietary ratio of omega-6 PUFAs to omega-3 PUFAs in the typical Western diet has dramatically increased from 4:1 to 25:1 over the past 50 years due to changes in agricultural practices that emphasized production. Domestic cattle have been largely grain-fed (a rich source of omega-6 fatty acids), which promotes greater and faster weight gain than cattle allowed to pasture. Additionally, post-World War I industrial innovations streamlined the production of vegetable oils for cooking and these oils were predominately composed of omega-6 fatty acids. This, coupled with studies demonstrating the hypolipidemic effects of corn oil (primarily omega-6 PUFAs) in the 1950s, resulted in displacement of other fats such as lard and butter in the U.S. diet.[8] Although it is now recognized that dietary omega-6 fatty acids (primarily linoleic acid) favor oxidative modification of LDL-cholesterol and increase platelet response to aggregation, there remains a dietary preponderance relative to omega-3 PUFAs.[9]

Since omega-6 fatty acids are subunits of arachidonic acid, a primary inflammatory precursor, an increase in dietary concentration favors formation of a group of eicosanoids with proinflammatory, prothrombic, and vasoconstricting effects such as tumor necrosis factor alpha (TNF alpha), thromboxane A2, prostaglandin E2, and leukotriene B4.[10]

Conversely, the omega-3 fatty acids EPA and DHA are precursors to a group of eicosanoids that have anti-inflammatory, antithrombotic, and vasodilatory effects. Such omega-3-derived eicosanoids include leukotriene B5, thromboxane A3, and prostaglandin E3. When

dietary ingestion of fatty fish and fish oil is increased, the EPA component competitively inhibits arachidonic acid metabolism, which results in the synthesis of less thrombogenic and less inflammatory eicosanoids. This change in the milieu of inflammatory mediators can decrease the risk of pathologic events in vascular beds throughout the body.[11] Clinical studies, both epidemiological[12] and prospective randomized trials, particularly secondary prevention trials, have shown a decrease in clinical CV events after increased fish oil supplementation or fish consumption equivalent to 1 g/d of EPA + DHA.[13,14] A primary intervention trial showed a significant decrease in inflammatory markers hsCRP, TNF alpha, interleukin-6, and leukotriene B4 for the group of patients treated with 1.4 g/d of fish oil capsules compared to placebo.[15]

Additionally, omega-3 fatty acids and their derived eicosanoids appear to bind to and regulate a group of transcription factors, the peroxisome proliferator-activated receptors (PPAR) alpha and gamma, both of which have been shown to inhibit the activation of inflammatory genes responsible for the formation of TNF alpha, IL-1beta, IL-6, inducible NO synthase, matrix metalloproteinases, and acute-phase proteins such as CRP. Thus, these PPAR receptors link dietary fat concentrations to glucose, lipid, endothelial, and immune homeostasis, which have important ramifications for clinical CV events.[16]

Cholesterol and Depression

The use of rosuvastatin in the JUPITER study significantly reduced levels of CRP, as well as lowering cholesterol levels already considered by primary prevention standards to be low. Such low cholesterol levels raise the concern as to whether there will be an increase in depression and suicide for such populations. This concern stems from analyses of mortality rates in primary prevention trials, which revealed an association between low cholesterol levels and suicide rates.[17,18] However, the exact association is not clear and there is no consensus from clinical trial results: While some studies support this finding,[19] other studies have shown no association between low cholesterol levels and suicide rates[20] and some, like Tanskanen et al,[21] demonstrated a relationship between elevated cholesterol levels and increased rate of violent suicide.

Lower serotonergic function may account for the link between diminished cholesterol levels and depression. Scanlon et al have shown in in vitro studies that a depletion of neural membrane cholesterol modulates serotonin transporter activity.[22] There may be some evidence for this in an autopsy study by Lalovic et al, which demonstrated decreased brain grey matter cholesterol in violent suicide victims.[23]

Given the complex relationship between suicidal risk, attempts, and suicidal death, and the multiple factors that influence cholesterol levels, it has been suggested that perhaps cholesterol is a surrogate marker of dietary PUFAs changes that have been linked to depression, one of the strongest risks for suicide.[24] This is why it may be important to consider modifying dietary PUFA composition, particularly to decrease the omega-6:omega-3 ratio as initial treatment of elevated inflammatory biomarkers vs initial use of statins for primary prevention. Statins are expensive medications that may have significant side effects such as muscle pains and liver enzyme abnormalities and may increase the risk for diabetes, a small but significant adverse effect noted in the statin treatment group of the JUPITER trial. Interestingly, Weidner et al found that patients on a low-cholesterol diet had reductions in depression if they increased fish consumption.[25] This suggests that differences in the dietary composition of PUFAs might explain the conflicting findings in the studies examining low cholesterol and rates of depression and suicide.

Omega-3 Fatty Acid Intake Recommendations

The American Heart Association recommendations for persons with known CHD are to eat one fatty fish meal at least twice a week or take 1 g/d of omega-3 PUFAs (EPA + DHA).[26] There is a standardized prescription formulation of omega-3 fatty acid ethyl esters called Lovaza® available in 1 g liquid-filled gel capsules, each of which contains 465 mg of EPA and 375 mg DHA.[27] It is currently, however, only FDA approved for treatment of significant hypertriglyceridemia, but as a result of JUPITER findings it may be a recommendation for persons with elevated levels of hsCRP. Indeed, instead of putting everyone on statins, it may be of greater benefit to increase dietary intakes of omega-3 PUFAs.

The Role of Periodontitis

Periodontitis is a local inflammatory process that causes destruction of the supporting gum and ligamentous tissue that anchors the teeth in alveolar bone. Although once thought to be a local process that was wholly the concern of dentists and other oral health practitioners, it is now clear that periodontal diseases play an important role in numerous conditions that impact CV health. The local oral mucosal response to the elaboration of lipopolysaccharides by the periodontopathic anaerobes in the gingival pockets causes infiltration of the periodontal tissues with inflammatory

cells including polymorphonuclear neutrophils, macrophages, and lymphocytes. Such activated macrophages release cytokines, which destroy oral connective tissue and alveolar bone and activate a systemic acute-phase response with an increase in inflammatory biomarkers such as CRP. The vascularity of the oral cavity ensures systemic dissemination of periodontopathic bacteria such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, which have been found in atherosclerotic plaques.[28,29]

Elevated CRP serum levels in patients with periodontal disease (PD) have been demonstrated in several studies.[30,31] A meta-analysis of several cross-sectional, prospective cohort and case-control studies found that after adjustment for smoking, diabetes, alcohol use, obesity, and blood pressure, subjects with PD had a 1.1-1.6 greater risk for developing CHD compared to those without PD.[32] Treatment of periodontitis results in a significant decrease in serum CRP levels[33] and an improvement in endothelial function.[34] The fact that PD is treatable and preventable through a regular regimen of brushing, flossing, and professional dental care suggests that to modify this risk factor for inflammation and CVD there is a need to get back to basics and educate patients about the importance of a daily routine of oral hygiene to general health.

Conclusion

Primary care physicians who see patients daily in the office for routine and urgent care are uniquely positioned to identify persons who are at risk for cardiovascular disease. Although dental and dietary assessments may not have been part of a physician's medical school training, they are now part of the on-the-job continuous learning process that is necessary to promote cost-effective dietary and lifestyle interventions that will not only modify a patient's cardiovascular risk factors by decreasing systemic inflammation, but also will improve their overall general medical health. ❖

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Yogurt and You? Probiotics and Infant Atopic Dermatitis

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PROBIOTICS ARE OFTEN THOUGHT OF AS CONCENTRATED yogurt capsules, most useful for the prevention or treatment of antibiotic-induced diarrhea. Recent evidence, though, is starting to point to a much greater use for the provision of "good bacteria" to the gastrointestinal tract. This article will review some of the connections between maternal and newborn probiotic intake and the prevention of infant atopic disease; which children might benefit from probiotic supplementation; and the nuances of probiotic dosing.

Definition

Probiotics are generally known as live, nonpathogenic microbial food ingredients beneficial to health when provided in adequate amounts.[1-3] The term "probiotic" is a general term that may refer to bacteria such as *Lactobacilli* spp. or *Bifidobacteria* spp. or yeast such as

Summary Points

- Probiotics are generally known as live, nonpathogenic microbial food ingredients beneficial to health when provided in adequate amounts.
- The composition of the intestinal microflora is different in children with atopic dermatitis; specifically, such children may have decreased levels of normally occurring *Bifidobacteria.*
- Clinical trials examining the effects of probiotics on atopic disease have been conducted in two main ways: supplementing pregnant women and then newborns, or focusing the probiotic supplementation on newborns at risk of atopic disease.
- Clinical results have been mixed; it is possible that the exact strain and dose used determines clinical efficacy (*Lactobacillus rhamnosus* GG dosed at 10 billion cfu per day was the dose in one positive clinical trial).

Saccharomyces boulardii. Probiotics may be found in dietary supplements (most commonly capsules) or fortified foods such as yogurt or milk.

Mechanism of Action

The idea to use beneficial bacteria in the treatment of atopic disease is not necessarily intuitive, but there has been a lot of research to support this line of thinking. Some of the idea behind using probiotics for this condition stemmed from data showing that the composition of the intestinal microflora is different in children with atopic dermatitis; specifically, such children may have decreased levels of normally occurring *Bifidobacteria*.[1] Even the well-documented gastrointestinal effects of probiotic therapy, such as improved IgA immune function, improvements in intestinal barrier function and pathological permeability, and changes in the presence or absence of certain bacteria, may be relevant to atopy.[1,2]

By improving abnormal intestinal permeability, probiotics may help to modulate the immune system, improving symptoms of atopic disease.[1] Also, in early childhood, probiotics may decrease excessive immune responses to foreign antigens, thereby affecting immune tolerance and the extent to which atopy develops.[4] This may be particularly important at early ages, when the gastrointestinal tract, immune system, and resulting allergic responses are in development.[2] Furthermore, probiotics may also help to balance pro-inflammatory and anti-inflammatory cytokines, contributing to decreased overall inflammation, in addition to helping process macromolecules in the intestinal tract, and decreasing dietary antigen loads.[2,4]

A "hygiene" hypothesis may explain why probiotic supplementation benefits atopic disease: There may be an increase in atopic diseases due to decreased human exposure to commensal organisms and resulting changes in immune system function.[3] Supplementation with probiotics may simulate the exposure to these commensal organisms, leading to increased Th1 and decreased Th2 T-cell responses and resulting in a calming of allergic and autoimmune diseases.[3,5] A clinical trial, however, did not find an effect on various immune system parameters in cord blood of newborns delivered to women who had been given 18 billion colony-forming units (cfu) *Lactobacillus rhamnosus* GG daily from 36 weeks gestation onward.[6] One ongoing clinical trial is further examining the potential of probiotic supplementation during infancy to prevent asthma.[7]

Clinical Trials: Pregnancy and Post-natal

Overall, among all clinical trials, the results have been mixed for the effectiveness of probiotics on childhood eczema. Many variables may account for this, but one expert points out that the clinical effect of probiotic supplementation varies greatly between species of bacteria used, dose administered, and whether there was adequate exclusion of probiotic intake from foods; these three variables in particular are important to consider when assessing probiotic clinical trials.[1]

A series of research trials has explored the hypothesis that the establishment of beneficial bacteria in the newborn may occur either in utero or during the early post-natal period. For example, one double-blind study randomized 159 women with a family history of atopic disease to take either capsules of *Lactobacillus rhamnosus* GG (10 billion cfu) or placebo beginning four weeks prior to delivery, and then for six months post-natally during breastfeeding or administered to the child with a spoon if not breastfeeding. The 132 children in the active group who completed the study at year 2 had half the incidence of atopic eczema (relative risk [RR] = 0.51),[8] while the 107 at the year 4 follow-up also had significantly less atopic eczema (RR = 0.57).[9]

A similar approach to pre- and post-delivery probiotic therapy was taken in 1,223 women (either the woman or the father of the baby needed to have diagnosed atopic disease) at 35 weeks of gestation who were prescribed a probiotic mixture (5 billion cfu each of *Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve*, and *Propionibacterium freudenreichii* ssp. *shermanii*) or placebo, and then instructed to administer the same preparation to the newborn every day for six months.[10] Of the 1,223 original entrants, 1,018 underwent intention-to-treat analysis, and 925 returned for follow-up at two years. The researchers separately analyzed for allergic diseases and IgE-associated atopic diseases using skin prick and blood tests. Physicians examined each newborn for atopic dermatitis at three, six, and 24 months, finding that eczema occurred less frequently in the probiotic group (odds ratio = 0.74) with a number needed to treat to prevent eczema of 16. The main side effects (abdominal discomfort, vomiting, and excessive crying) occurred in equal amounts among the placebo and treatment groups.

Using a protocol similar to the previous studies, 105 German women with a family history of atopic disease were randomized to 5 billion cfu *Lactobacillus* GG or placebo for 4-6 weeks before expected delivery and for six months afterwards; the main outcome being studied was the incidence of atopic dermatitis in the newborn at 2 years of age.[11] No difference was found in the risk or severity of atopic dermatitis in the two groups, making the researchers doubt the effectiveness of probiotic supplementation in primary prevention of atopic dermatitis.

Two factors in this study differed from the previously mentioned research and may account for this result: The patients in this study had a more significant family history of atopy, and, a very preliminary hypothesis, were of a different genetic background (other studies examined Finish and Australian women and newborns) possibly with less susceptibility to the effects of probiotics.

Clinical Trials: Newborns

One review of 12 clinical trials involving 781 children with eczema found significant variety in the results of individual trials, which the reviewers mentioned could be due to different strains and doses used.[1] Five of the trials used symptom scores and 10 rated eczema severity; none of the trials showed a difference between probiotic and placebo groups (P = 0.33-0.36). Interestingly, subgroup analyses revealed a worsening of eczema (higher SCORAD, an eczema rating system) with *Lactobacillus* GG vs placebo (P = 0.02), but an improvement symptoms with other *Lactobacillus* species ($P < 0.01$).

One example of a double-blind clinical trial randomized 27 breastfed infants (average age, 4.6 months) with atopic dermatitis after weaning to three types of formula: a hydrolyzed whey formula, or the same formula supplemented with either 1 billion cfu/g *Bifidobacterium lactis* Bb-12, or 0.3 billion cfu/g *Lactobacillus* GG (ATCC 53103).[2] After two months, a skin condition rating system demonstrated a significant improvement in the probiotic groups compared to the placebo group (P = 0.002). Furthermore, statistically significant immune system changes were seen only in the probiotic-supplemented groups; there were decreases in serum CD4 (P = 0.005), changes (decreases with *Bifidobacterium* and increases with *Lactobacillus* GG) in serum TGF-beta1 (P = 0.007), and decreases in urine eosinophilic protein X (a reflection of allergic inflammatory activity in atopic disease such as asthma) in both probiotic groups (P = 0.01-0.04). Other immune parameters were unaffected, and the researchers did not mention any adverse effects.

A randomized, double-blind trial in 231 newborns of mothers with atopic disease compared 6 months of *Lactobacillus acidophilus* (3 billion cfu) to placebo, and found similar rates of atopic dermatitis at age six and 12 months, though only 178 infants completed the trial.[5] Allergen skin prick testing and atopic dermatitis was higher in the probiotic group at the 12-month check (P = 0.045), as was sensitization to common allergens when assessed at 12 months (P = 0.030).

A more complicated examination of this topic was undertaken in 230 infants suspected of having cow's milk allergy.[12] They were randomized to *Lactobacillus rhamnosus* GG (5 billion cfu), a mixture of probiotics (5 billion cfu *L. rhamnosus* GG, 5 billion cfu *L. rhamnosus* LC705, 200 million cfu *Bifidobacterium breve* Bbi99, and 2 billion cfu *Propionibacterium* JS), or placebo, and all placed on an cow's milk elimination diet plus topical skin treatments. At the end of eight weeks, each group was subjected to a double-blind cow's milk rechallenge, and skin symptom scoring was recorded. All groups improved (similarly so) over the course of the study, presumably from the removal of cow's milk from the infants' diet. The only subgroup showing improvement after milk rechallenge was in the *Lactobacillus rhamnosus* GG group for infants with IgE-associated atopic dermatitis (P = 0.036).

Dose

General dosing is mentioned in some sources, such as a minimum of 5-10 billion cfu for children.[4] Many experts recommend dosing based on a specific strain or patented product as per clinical trials. Such a recommendation, if based on the clinical trials with a positive effect on atopy, would lead to daily doses of 5-10 billion cfu in the case of *Lactobacillus rhamnosus* GG. In some cases probiotic mixtures were used in clinical trials, usually with doses of 5 billion cfu of each species, such as *Lactobacillus rhamnosus* GG, *Bifidobacterium breve*, and *Propionibacterium* species.

As a side note, many "therapeutic" yogurts and fermented milks exist and provide some of the same probiotic species seen in clinical trials and basic science research. For example, Activia® provides *Bifidobacterium animalis*, Danactive™ provides 10 billion cfu of *Lactobacillus casei* per serving, and Yoplait® Yo-Plus has 1 billion cfu of *Bifidobacterium lactis* per serving.

Adverse Effects

Probiotics are considered safe in healthy individuals;[2] the adverse effects described below (sepsis, bacteremia, fungemia) have not appeared to occur in otherwise healthy people.[13] Literature reviews reveal several dozen case reports of bacteremia/fungemia and sepsis in both children and adults who were taking probiotics. In most of the cases there were identifiable risk factors (gastrointestinal pathology, diabetes, recent surgery, cancer); also, not all of the cases had definitively identified the suspect strain nor proven cause and effect.[1,3,13] For example, it can be difficult to assess whether *Lactobacillus* sepsis occurs from normal flora or from ingested probiotics.[14]

However, as a result of these data, some researchers list contraindications for probiotics, such as anyone with underlying immune system dysfunction, chronic disease, or "debilitation."[13] This recommendation is anything but

certain, given that some studies show that probiotics are safe for use in people with HIV, and may even prevent necrotizing enterocolitis in preterm neonates despite their often immunocompromised state.[14]

For children that have a cow's milk allergy, it is important to use only products that are milk-free; if not, there is the possibility of exacerbation of allergic symptoms.[15]

Of note, there is huge variety in the quality of probiotic supplements. One study of 20 refrigerated (n = 12) and non-refrigerated (n = 8) *Lactobacillus* products from commercial sites in Seattle found that 30% of the products grew contaminant bacteria species in laboratory culture media, and 20% had no growth at all.[16] Some of the contaminants contained gram-negative rods, *Bacillus* species, and *Enterococcus* species, potentially harmful with ingestion.

Conclusion

Probiotics are live microbial food supplements that, in adequate amounts, provide a health benefit beyond basic nutrition. Supplementation with certain strains can then populate the intestinal tract, possibly decreasing pathological intestinal permeability and the passage of antigens into the systemic circulation. The hypothesis, and there is some immunological data to support this, is that select bacteria can cause beneficial changes in immune system function and allergic responses to antigens that lead to a benefit in atopic dermatitis.

Clinical trials have been conducted in two main ways: supplementing pregnant women and then newborns, or focusing the probiotic supplementation on newborns at risk of atopic disease. Results have been mixed, with some showing improvements in the incidence of atopic dermatitis, while others have shown no difference. It is possible that the exact strain and dose used determines clinical efficacy; *Lactobacillus rhamnosus* GG dosed at 10 billion cfu per day was the dose in one positive clinical trial. Adverse effects, the worst being sepsis or bacteremia, seem limited to people with immune system pathology or chronic disease.

Recommendation

The research on probiotic supplementation in childhood atopic dermatitis is in its infancy, no pun intended. Interesting basic science has delineated a compelling mechanism of action, and some clinical trials are showing benefit when pregnant women and/or newborns are supplemented with probiotics, most convincingly at a dose of 5-10 billion cfu daily of *Lactobacillus rhamnosus* GG, *Bifidobacterium breve*, and *Propionibacterium* species, either separately or as a mixture. There is variety in clinical response across populations, perhaps with a genetic basis for why one group responds to probiotic supplementation, while another shows no change or even worsens. Close clinical monitoring is warranted, and only products that have been subject to third-party verification or those used in clinical trials should be incorporated into clinical practice. ❖

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Massage for Pain and Anxiety in Cancer Patients

By Dónal P. O'Mathúna, PhD

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THIS ARTICLE IS A CONTINUATION OF LAST MONTH'S examination of reflexology for cancer patients. Massage is one of the most commonly used non-pharmacological interventions for managing cancer pain.[1] In the often-cited surveys conducted by David Eisenberg and colleagues, after prayer for healing was excluded, massage was the third most commonly used complementary therapy in the United States in 1997 and 1990.[2] In his survey conducted in 2002, massage had fallen to sixth in popularity, having been used by 5% of the U.S. population in the previous year compared to 11.1% in 1997.[3] Reasons for this change were not proposed but the numbers remain significant.

For cancer patients, massage is said to reduce anxiety, stress, pain, muscle tension, and fatigue.[4] Such benefits would be of great value to many cancer patients. About one in five U.S. cancer patients seek massage, and approximately 70% of hospices in the U.K. provide massage.[5] Clinicians may expect to be asked by patients with cancer whether massage is likely to be beneficial for them. The evidence available to address such questions will be reviewed here.

Background

Massage is an ancient therapy that has long been valued. Hippocrates wrote that, "The physician must be experienced in many things, but assuredly in rubbing," i.e., massage. Toward the end of the 19th century, massage experienced a resurgence as nurses included it in their care of patients.[6] A debate broke out in the *British Medical Journal* and then the public press alleging that massage had become entwined with prostitution and did not belong in medical establishments. A professional organization was born from this debate that developed standards for massage and went on to become the forerunner of the physical therapy profession. However, the link with medical care had been severed, which only recently has begun to be re-established.

Many different types of massage are practiced. Common to all forms is manipulation of the body's soft tissues by the massage therapist's hands to affect the vascular, muscular, and nervous systems.[4] The most widely used form of massage used in health care settings is Swedish massage in which the hands move over the skin in long, gliding strokes (also called "effleurage").[7] The muscles may be kneaded and light friction may be applied to the skin. Oil or lotion is often applied as a lubricant and to provide aromatherapy. Rolfing is a form of deep tissue massage where additional pressure is applied to the fascia to promote full range of motion and restore elasticity to connective tissue.[8] Shiatsu massage is another deep form of massage which developed in Japan under the influence of traditional Chinese medicine. Various acupoints are massaged using the practitioners' fingers, thumbs, palms, or elbows, even knees or feet.

Mechanism of Action

The precise mechanism of action by which massage may have physical or psychological benefits has not been established. One proposal is that massage triggers a generalized positive reaction to human touch that is essential for health and well-being.[5] It may directly relieve muscular aches and tension. Massage can also increase the temperature and blood flow to tissues being manipulated, which is said to promote healing. Little research has been conducted to establish whether any or all of these mechanisms are involved in any beneficial effects.

Clinical Studies

Much of the evidence available for using massage with cancer patients is anecdotal. A systematic review of research on massage with cancer patients was conducted

Summary Points

- The evidence for massage benefiting cancer patients is relatively weak and somewhat contradictory.
- Some evidence supports the use of massage to relieve pain and anxiety in cancer patients.
- Cancer patients appear to tolerate massage well, even when at advanced stages, provided care is taken to avoid obviously sensitive parts of the body.

using the Cochrane Collaboration approach in 2003 and updated in 2006.[4] Ten randomized controlled trials (RCTs) were identified. A meta-analysis was not possible because of differences in the type of massage used and the design of the studies. The results were inconsistent, with some finding improvements in pain, nausea, anxiety, and other symptoms, but other studies failing to find significant improvements. Overall, the methodological quality was rated as generally poor according to the CONSORT criteria. Outcome assessors were blinded in only four of the trials. Allocation concealment was assessed as adequate in one trial and only two had adequate randomization methods. Sample sizes ranged from six to 87 participants. The reviewers determined that definitive conclusions on the effectiveness of massage for cancer patients could not be drawn from these studies. However, they noted that there was limited evidence of improvement in pain symptoms and short-term psychological well-being.

Another systematic review included studies which did not include control groups.[1] An additional five quasi-experimental studies were located. This review carried out retrospective power calculations on all the studies reviewed. An acceptable level of power is generally 0.80 or higher, indicating an 80% probability of the correct conclusion. In many of the studies reviewed, the power was in the range 0.1-0.4, indicating inadequate sample sizes. For example, one study enrolled 28 participants, yet to detect a significant difference between the two groups they would have needed 326 participants in each group to achieve a power of 0.80. Another study needed 160 participants, but only recruited 29. This systematic review concluded that "the methodological flaws prevent conclusions about the efficacy of massage in cancer patients."

One study has been conducted with a large number of participants (n = 1,290); however, this study did not have a control group.[5] Patients in a large cancer center could refer themselves or be referred by health care professionals for three types of massage: Swedish massage, light touch massage, or foot massage. Before and after massage, patients scored themselves on visual analog scales for six separate symptoms. After adjusting for baseline scores, all symptoms were improved: stress/anxiety, by 52%; fatigue, 41%; pain, 40%; depression, 31%; nausea, 21%; and "other", 47%. The improvements were particularly pronounced for those who had more severe symptoms at baseline. Improvements like these have been found in a small number of similar studies.[9] However, the lack of control groups in these studies makes it impossible to attribute causation to the massage or other potential confounding factors.

The results of the largest RCT to date of massage with cancer patients were published recently.[10] The trial enrolled 380 patients with advanced cancer at 15 U.S. hospices. Patients received either individualized Swedish massage or a control intervention where the researcher's hands were placed for 3 minutes each on several sites around the body. Touch was light, with no movement of the hands. Pain, mood, and quality of life were measured before intervention, immediately after intervention, and weekly for three weeks. Statistically significant improvements in pain and mood were found after both massage and control intervention, but the changes might not be clinically significant. Massage was statistically superior to control ($P < 0.001$). The improvements were not sustained as no significant differences were found on any of the measurements made subsequent to those collected immediately post-intervention. Quality of life did not differ significantly between groups.

Adverse Effects

Massage usually does not elicit adverse effects, but this has rarely been studied. When cancer patients are given massage, some authors recommend avoiding the sites of tumors, bone metastases, medical devices, deep vein thrombosis, and open lesions.[1] However, in the recent large RCT with advanced cancer patients, no differences in adverse events or deaths were found between the massage and control groups.[10]

Conclusion

The evidence available to support the use of massage for the relief of pain and anxiety in cancer patients is weak. Relatively few controlled trials have been conducted, their quality is generally low, and the results are contradictory. However, studies without comparison groups have found that patients report significant benefits immediately after receiving massage. While those benefits are usually not sustained, they can be very important for cancer patients, especially those with advanced cancer. Those with the highest pain and anxiety scores tend to improve the most. While existing studies cannot show if the benefits are due to massage itself, or are a generalized feature of human touch and presence, massage may be of benefit for some cancer patients.

Recommendation

Massage may be a useful means of relieving pain and anxiety in some cancer patients. While the evidence from controlled trials is not strong, the potential for benefit, with little risk of adverse effects, makes massage a

suitable complementary therapy for some cancer patients. However, while some patients may be interested in massage, many are not. Researchers in one clinical trial found that many cancer patients refused massage, particularly male patients.[9] This may reflect a lack of familiarity with massage, or a concern for privacy, but should be taken into consideration when discussing massage. More research is needed to understand whether certain types or durations of massage may have more benefit than others. ❖

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CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. 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

1. Which of the following statements is *false* with regard to the JUPITER study?
   a. A decrease in hsCRP resulted in a decrease in clinical endpoints.
   b. Median baseline LDL-cholesterol levels were in the recommended treatment range.
   c. The study included a substantial proportion of women and minorities.
   d. The clinical benefits were observed in every subgroup.

2. Which of the following significant adverse effects was reported in the treatment group of the JUPITER study?
   a. Muscle pain
   b. Liver enzyme abnormalities
   c. Diabetes
   d. Depression

3. Clinical trials of probiotic supplementation for infant atopic dermatitis have shown best results when pregnant women and/or newborns are given 5-10 billion cfu daily of:
   a. *Lactobacillus rhamnosus* GG
   b. *Bifidobacterium breve*
   c. *Propionibacterium* species
   d. Any of the above separately or as a mixture

4. The most commonly used form of massage in health care settings is:
   a. rolfing.
   b. shiatsu massage.
   c. Swedish massage.
   d. tai chi.

5. Among the general U.S. population, recent surveys have found that massage:
   a. is rarely viewed as beneficial.
   b. is one of the more popular complementary therapies.
   c. is the most commonly used complementary therapy.
   d. has not been used.

Answers: 1. b, 2. c, 3. d, 4. c, 5. b.

What's That Herb Again...? Ginkgo for Dementia

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *A well-regarded, standardized extract of* Ginkgo biloba *does not appear to help prevent development of dementia in seniors with baseline normal or mildly impaired cognitive function. Whether use of ginkgo earlier in life has a primary preventive effect on development of dementia remains to be determined.*

Source: DeKosky ST, et al. *Ginkgo biloba* for prevention of dementia: A randomized controlled trial. *JAMA* 2008;300: 2253-2262.

THE AUTHORS OF THIS MULTICENTER, RANDOMIZED, double-blind trial study (The Ginkgo Evaluation of Memory study) sought to determine whether use of a standardized extract of *Ginkgo biloba* over time would decrease the incidence of all-cause dementia, especially Alzheimer's disease, in people older than age 75 years. Participants (n = 3,069 total, n = 482 with mild cognitive impairment; mean age of all subjects = 79.1 years) had to have either normal cognitive function or mild cognitive impairment at baseline. Subjects were randomized to receive either 120 mg *Ginkgo biloba* extract (EGb-761) or an identical placebo tablet twice daily. They were then assessed every six months for incident dementia using multiple tests and scales, and employing DSM-IV criteria. If a diagnosis of dementia was being considered, additional neurologic work-up was undertaken, including MRI scanning, to exclude atypical etiologies of dementia.

After a median follow-up of 6.1 years, a total of 523 people developed dementia, with 92% of them being classified as having Alzheimer's disease or Alzheimer's disease with concomitant vascular disease. Overall dementia rates were 3.3/100 years in the active group and 2.9/100 years in the placebo group. The hazard ratio for ginkgo use and all-cause dementia was 1.12, and 1.16 for Alzheimer's disease compared with placebo. Adverse events were similar in both groups, and rates of major bleeding did not differ statistically, but there were twice as many hemorrhagic strokes in the ginkgo group than in the placebo group (16 vs 8); however, the numbers were very small. The authors conclude that a standardized extract of *Ginkgo biloba* given in a commonly used dose does not reduce the overall incidence of dementia in seniors with normal cognitive function or those with MCI.

■ COMMENTARY

This is a very well-done trial using a well-standardized extract of *Ginkgo biloba* and employing comprehensive assessments of cognitive status to support or refute a diagnosis of dementia in senior citizens. The methodology is sound even though compliance was only about 60% by trial's end. The sample size is significant, follow-up was superb, and lots were tested individually and identified. EGb-761 has been well-studied and is considered by most experts the standard by which other ginkgo extracts must be measured. The problem comes in how to interpret the data in the context of younger patients who might be at risk for dementia.

Since the study only addressed individuals older than age 75 we do not know, as the authors rightly point out, whether a longer duration of ginkgo administration started earlier in life would have offered a primary preventive effect. Thus, the results seem clear only in that older individuals should not use ginkgo to try to stave off dementia. As for those of us still in our prime, whether that's true or just in our minds (cognitively, of course), the question of ginkgo's potential utility remains to be answered.

Truly effective treatments to prevent or delay the onset of dementia, and to preserve cognitive function, have yet to be identified. The current study contributes to our understanding in a select population but not to younger people, where preventive strategies may be most effective. ❖