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Aspirin and Cancer Prevention

ABSTRACT & COMMENTARY

By Howell Sasser, PhD

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

Synopsis: *Aspirin is a common preventive agent for cardiovascular disease. Its use for cancer prevention has been studied for many years, but meta-analytic results were lacking until now. An international group reports findings from analyses of short- and long-term outcomes of aspirin use for cancer prevention. Key findings are a reduced risk of short-term incidence of and death from cancer, and a reduced risk of long-term incidence of some kinds of cancer and distant metastasis. With a few caveats, these results strengthen the case for aspirin as a tool in cancer prevention.*

Sources: Rothwell PM, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* Published online March 21, 2012.

Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomised trials. *Lancet* Published on-line March 21, 2012.

THE ROLE OF ASPIRIN IN THE PREVENTION OF CARDIOVASCULAR DISEASE events is well known.[1,2] The recommendation of daily low-dose aspirin (< 100 mg/day) is common, though not without clinical concern because of the potential side effect of bleeding events.[3] This and other issues have motivated an ongoing body of observational and interventional research representing a large number of people. This resource has now been recruited for secondary analyses of aspirin and cancer risk.

Aspirin has been hypothesized to influence cancer incidence, metastasis, and mortality by altering platelet function, by inhibiting

Summary Points

- Aspirin has been hypothesized to influence cancer incidence, metastasis, and mortality by altering platelet function, by inhibiting the COX-II enzyme's role in inflammation, or by promoting programmed cell death.
- Analyses of short- and long-term outcomes of aspirin use for cancer prevention show a reduced risk of short-term incidence of and death from cancer, and a reduced risk of long-term incidence of some kinds of cancer and distant metastasis.
- Aspirin appears to confer at least a modest degree of protection from cancer without a large increase in the risk of side effects.

the cyclooxygenase-II (COX-II) enzyme's role in inflammation, or by promoting programmed cell death (apoptosis).[4,5,6] These relationships have been explored in laboratory settings since at least the late 1960s. The difficulty in showing such a mechanism in vivo relates to the relative rarity of cancer — especially any specific type of cancer — and to the modest size of the expected protective effect of aspirin. These were among the challenges addressed and largely overcome in recent articles published in the *Lancet* by an international group of researchers.[7,8]

Briefly, the group published the results of analyses of the short-term (up to 10 years) and long-term (up to 20 years or more) effects of regular aspirin treatment, in which they combined and summarized the findings of many individual studies. The analysis of short-term effects used data from clinical trials designed to assess the effect of aspirin in preventing vascular events, with cancer cases reported as incidental findings. The analysis of long-term effects was based on original studies, both clinical trials and observational designs, focusing directly on aspirin and cancer risk.

The short-term analysis included trials testing aspirin regimens of any dose, in the absence of any other antiplatelet therapy, although a "background of anticoagulation" was permitted. It excluded those with treatment durations of less than 90 days. Those receiving aspirin and not receiving it were pooled into groups and analyzed using appropriate meta-analytic methods. The outcomes of interest were cancer incidence, death from cancer, and non-vascular death (included because some trials specified the cause of death only as vascular or non-vascular in origin).

There was a reduced risk of death both when the analysis was limited to known cancer deaths (odds ratio [OR] = 0.85, $P = 0.008$), and when non-vascular deaths were included as well (OR = 0.85, $P = 0.005$). When deaths were grouped by duration of follow-up (0-2.9 years, 3-4.9 years, ≥ 5 years), there was a reduced risk with aspirin in all intervals, but it became statistically significant only after 5 years of follow-up. There was also a reduced incidence of cancer among those treated with aspirin (hazard ratio = 0.88, $P = 0.017$), and a similar pattern of stronger protection with longer duration of treatment was noted.

The long-term analysis cast a wider net, including both observational and experimental studies published between 1950 and 2011, but only those in which aspirin's effect on cancer was the primary focus. The definition of aspirin use was necessarily different across study types. In the clinical trials, an aspirin/no aspirin comparison was possible. In the observational studies, categories of "Any aspirin" and "Maximum reported aspirin" were used when it was not possible to determine the dose or frequency of aspirin use. A study might qualify under more than one method of categorization. A number of individual cancer types were analyzed separately, of which colorectal cancer was numerically the largest. The outcomes of interest were cancer incidence and metastasis. Studies were pooled by type (clinical trial, case-control, cohort, or nested case control) and analyzed with meta-analytic methods.

There was a statistically significant reduction in the risk of colorectal cancer across all study types and almost all definitions of aspirin use (risk reductions between 13% and 49%, P-values between 0.012 and 0.0001). There

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Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com.

were also significant reductions in biliary, esophageal, gastric, and breast cancers with any aspirin use seen in the observational studies. The numbers of cases in the clinical trials, and for other kinds of cancer, were often too small to permit stable estimation of risk. Aspirin use was associated with a reduced risk of distant metastasis (OR = 0.69, $P < 0.0001$), but not more local spread of cancer.

Taken as a whole, these results are important for a number of reasons. First, they include information from numerous studies done over many years. This limits the impact of study-specific conditions or secular changes that might be difficult to recognize, let alone control for, in an individual study. Second, they show generally good agreement between the findings of observational and experimental research in this area. This serves to validate the results of the much more numerous observational studies, enabling us to rely on them more than would otherwise be the case. Third, they show that at least over the long term, use of aspirin of any dose (and perhaps even with less than daily frequency) confers some protection, even if it is not as great as that seen with daily use.

There are, however, a few limitations in these studies worth noting. The short-term studies were not originally designed to focus on cancer. This may have had an impact on the quality of their collection of cancer data and certainly limits their precision whenever specific causes of death were not recorded. The heterogeneity of dosing in the clinical trials, and the uncertainty about both the amount and frequency of aspirin use in the observational studies makes it difficult to draw conclusions about what to recommend to patients. The potential benefit of aspirin in prevention of adverse health events must be balanced against the risk of bleeding. In all of the studies, the possibility exists that participants used "unprescribed" over-the-counter aspirin, although if anything this should weaken the apparent associations.

These findings strengthen the case for regular use of aspirin in the prevention of cancer. It appears to confer at least a modest degree of protection without a large increase in the risk of side effects. As with any other preventive strategy, patients should be cautioned that aspirin is only one part of a complete medical and lifestyle program. It should not be used to offset other modifiable risk factors. Used realistically, however, it does appear to be a valuable tool in the promotion of health and prevention of disease. ■

References

1. Hennekens CH, et al. Aspirin as a therapeutic agent in cardiovascular disease: A statement for healthcare professionals from the American Heart Association. *Circ* 1997;96:2751-2753.
2. U.S. Preventive Services Task Force. Aspirin for the Prevention of Cardiovascular Disease: U.S. Preventive Services Task Force Recommendation Statement. *Ann Int Med* 2009;150:396-404.
3. Berger JS, et al. Aspirin for the primary prevention of cardiovascular events in women and men: A sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;295:306-313.
4. Gasic GJ, et al. Anti-metastatic effect of aspirin. *Lancet* 1972;300:932-933.
5. Wang D, Dubois RN. Prostaglandins and cancer. *Gut* 2006;55:115-122.
6. McIlhatton MA, et al. Nitric oxide-donating aspirin derivatives suppress microsatellite instability in mismatch repair-deficient and hereditary nonpolyposis colorectal cancer cells. *Cancer Res* 2007;67:10966-10975.
7. Rothwell PM, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* Published online March 21, 2012.
8. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomised trials. *Lancet* Published online March 21, 2012.

Probiotics for the Treatment of Vulvovaginal Candidiasis

By Donald Brown, ND

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

Vulvovaginal candidiasis (VVC) is a common infection that afflicts an estimated 75% of sexually active women at least once in their life,[1] and of these, approximately 50% will develop a second episode, with 5% suffering recurrent VVC (defined as four or more episodes within a 1-year period).[2] A 2000 survey in the United States found that 6.5% and 8% of women older than 18 years reported one and four episodes of VVC during the 2 months and 1 year prior to the survey, respectively.[3] VVC is the second most common cause of vaginal infections after bacterial vaginosis (BV). In a 1995 U.S. report, VVC

Summary Points

- Vulvovaginal candidiasis (VVC) is a common infection that afflicts an estimated 75% of sexually active women at least once in their life.
- Many of the relevant studies on the use of probiotics for the prevention of recurrent VVC have methodological problems; therefore, supportive evidence is limited.
- Despite these shortcomings and questions, the use of probiotics seems a low-risk practical consideration for this patient population.

diagnosis and treatment, together with lost productivity, resulted in an estimated cost of $1.8 billion.[1]

VVC is diagnosed by the presence of a thick, white vaginal discharge in association with vulvar itching, burning, and/or dysuria, in addition to normal vaginal pH (< 4.5), presence of hyphae, pseudohyphae, or budding yeasts visualized under optical microscopy in wet mount preparations with 10% potassium hydroxide, visualization of fungi constituents after Gram-staining the vaginal sample, and growth of the micro-organism in selective culture media.[4,5] Even though treatment of VVC with a range of oral and intravaginal antifungal drugs is often effective, recurrence rates remain high. One issue related to recurrence is the finding that vaginitis induced by non-*albicans* species is clinically indistinguishable from that caused by *Candida albicans*, and these former species are often more resistant to standard drug treatment.[6]

Vaginal Microbiota and VVC

In a previous review article in this publication, an overview of the *Lactobacilli* species that dominate the vaginal mircoflora of healthy premenopausal women (principally dominated by *Lactobacilli* species, especially *Lactobacillus crispatus*, *L. gasseri*, *L. jensenii*, and *L. iners)* was provided.[7] Also noted in that article was the fact that there appears to be an inverse correlation between the presence of H_2O_2-producing *Lactobacilli* spp and risk of BV. It is interesting to note that this has not been clearly established in women with VVC. One study found that Lactobacilli were the dominant vaginal microorganisms in 90% of 20 healthy premenopausal women and 96% of 24 premenopausal women with acute exacerbations of recurrent VVC.[8] However, the vaginal microbiota was more commonly dominated by *L. salivarius* in healthy women while *L. catenaforme* was isolated more frequently in women with VVC. A study with 7,918 pregnant women found that VVC was associated either with normal vaginal microbiota (predominance of Lactobacilli) or a decrease in Lactobacilli.[9] Other studies have suggested that pregnant[10] or post-term women[11] whose vaginas were colonized with H_2O_2-producing Lactobacilli were less likely to have symptomatic VVC than those colonized with *Lactobacilli* spp that did not produce H_2O_2.

Probiotics for the Prevention and Treatment of VVC

A survey published in 2003 reported on 1117 women, ages 18-70 years, with self-reported VVC, found that Lactobacillus supplements were used by 40% and 43% of these women for prevention and treatment of post-antibiotic VVC, respectively.[12] The published clinical data to date have focused primarily on the use of probiotics for the prevention of VVC following antibiotics or in at-risk groups (e.g., HIV-positive) and women with a history of recurrent VVC. While this review will be more selective and focus primarily on two studies (one prevention and the other treatment), readers may want to review a meta-analysis published in 2006 by Falaga et al that focuses on prevention of recurrent VVC with probiotics.[13] The studies reviewed were published from 1992 to 2004 and include intravaginal and oral (including yogurt) administration of probiotics. The review suffers somewhat by the inclusion of studies that combine women with recurrent VVC and those with other types of recurrent urogenital infections. The authors conclude that many of the relevant studies have methodological problems (e.g., small sample size, no control group) and that the evidence for probiotics in prevention of recurrent VVC is limited. However, they add, "the empirical use of probiotics may be considered in women with frequent recurrence of VVC (more than three episodes per year), especially for those who have had adverse effects from or contraindications for the use of antifungal agents, since adverse effects of probiotics are very rare."

Prevention of VVC in HIV-Positive Women

A three-arm, multicenter, randomized, double-blind, placebo-controlled trial compared the ability of intravaginal *L. acidophilus* and clotrimazole to prevent VVC in HIV-positive women.[14] The study enrolled 164 women (ages 25-59 years old) who were HIV seropositive that were not pregnant or taking any antifungal medications. Subjects were randomized to one of three groups: 1) intravaginal *L. acidophilus* (2 x 10^9 cfu; Gynatren, Natren, Inc.); 2) clotrimazole powder (100 mg); or 3) placebo powder. Both active treatments were supplied in refrigerated capsules and women were instructed to insert one capsule vaginally once per week for 21 months.

During the 21 months of the study, 34 cases of

VVC were diagnosed clinically and microbiologically. Compared to the control group, the relative risk for developing VVC was 0.54 (95% confidence interval [CI], 0.26 to 1.13) for the probiotic group and 0.49 (95% CI, 0.22 to 1.09) for the clotrimazole group. The estimated median time to first episode VVC was longer for clotrimazole group ($P = 0.03$, log rank test) and the probiotic group ($P = 0.09$, log rank test) compared with the placebo group.

A detailed analysis of this study questions the significance of the clinical effect found for both treatment groups in the study.[15] They also criticize the study design for not confirming the presence of viable *Lactobacilli* spp in the vaginas of women in the probiotic group to confirm compliance, proper storage, and viability.

Adjunctive Use of Probiotics in Treatment of VVC

In a randomized, double-blind, placebo-controlled trial, 55 women (16-46 years old) with VVC were treated with a single dose of oral fluconazole (150 mg) and then randomized to receive either two capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (each capsule contained 1 x 10^9 cfu of each probiotic strain; Chr. Hansen, Horsholm, Denmark) or placebo orally in the morning for 28 days starting on the day of fluconazole use.[16]

At 4 weeks, the probiotic group exhibited cure of VVC as determined by having no vaginal discharge, itching and/or burning, dyspareunia and/or dysuria, and negative culture ($P < 0.05$). The probiotic treated group showed significantly less vaginal discharge (10.3% vs 34.6%; $P = 0.03$) and lower presence of yeast detected by culture (10.3% vs 38.5%; $P = 0.014$) compared with the placebo group. No significant adverse events were reported in either group.

Conclusion

Albert Döderlein first described the role of "bacillus" in the health of the female genitourinary tract in 1892. Long referred to as "Döderlein bacillus," we now know that the healthy vaginal flora is made up primarily of members of the *Lactobacillus* family. However, as opposed to the role of healthy vaginal flora in reducing the risk of BV, their role in the prevention of VVC is less clear.

The data on the use of probiotics for the prevention of VVC to date are equivocal; larger and better-designed clinical trials with established probiotic strains are needed to more clearly assess the potential efficacy of probiotics in women with recurrent VVC.

Although there is only the one published clinical trial to date that was reviewed above, the oral probiotic combination of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 appears to be an interesting candidate for future clinical trials in women with VVC. As was the case with two trials in women with BV, the use of this combination appears to improve treatment outcomes in women taking standard antimicrobial therapy. Future studies should also follow women for a longer period of time to determine whether this probiotic therapy may also reduce recurrence rates.

Recommendation

Women being treated for VVC with antimicrobial therapy should be informed about the potential benefits of adjunctive use of probiotics to help improve treatment outcomes and to re-establish healthy vaginal flora. Women interested in using probiotics for the prevention of VVC recurrences should be counseled about the equivocal clinical data to date. Despite these shortcomings and questions, the use of probiotics seems a low-risk, practical consideration for this patient population. ■

References

1. Ferrer J. Vaginal candidosis: Epidemiological and etiological factors. *Int J Gynecol Obstet* 2000;71(Suppl1):S21-S27.
2. Paulitsch A, et al. A 5-year (200-2004) epidemiological survey of Candida and non-Candida yeast species causing vulvovaginal cnadidiasis in Graz, Austria. *Mycoses* 2006;49:471-475.
3. Foxman B, et al. Candida vaginitis: Self-reported incidence and associated costs. *Am Sex Transm Dis Assoc* 2000;27:230-235.
4. Sheary B, Dayan L. Recurrent vulvovaginal candidiasis. *Aust Fam Physician* 2005;34:149-157.
5. Eckert LO, et al. Vulvovaginal candidiasis: Clinical manifestations, risk factors, management algorithim. *Obstet Gynecol* 1998;92:757-765.
6. Bauters TG, et al. Prevalence of vulvovaginal candidiasis and susceptibility to fluconazole in women. *Am J Obstet Gynecol* 2002;187:569-574.
7. Brown D. Probiotics for the treatment of bacterial vaginosis. *Altern Med Alert* 2012;15:25-29.
8. Sobel J, Chaim W. Vaginal microbiology of women with acute recurrent vulvovaginal candidiasis. *J Clin Microbiol* 1996;34:2497-2499.
9. Hillier SL, et al. Characteristics of three vaginal flora patterns assessed by gram stain among pregnant women. Vaginal infections and prematurity study group. *Am J Obstet Gynecol* 1992;166:938-944.
10. Rossel GA, et al. Fetal fibronectin and microorganisms in vaginal fluid of healthy pregnant women. *Acta Obstet Gynecol Scand* 1996;75:520-525.

11. Goffeng AR, et al. Microorgansims in vaginal fluid from women in prolonged pregnancy. *Gynecol Obstet Invest* 1997;44:16-20.

12. Pirotta M, et al. "Not thrush again!" Women's experience of post-antibiotic vulvovagnitis. *MJA* 2003;179:43-46.

13. Falagas ME, et al. Probiotics for prevention of recurrent vulvovaginal candidiasis: A review. *J Antimicrob Ther* 2006;58:266-272.

14. Williams AB, et al. Evaluation of two self-care treatments for prevention of vaginal candidiasis in women with HIV. *J Assoc Nurses AIDS Care* 2001;12:51-57.

15. Ray A, et al. Intervention for prevention and treatment of vulvovaginal candidiasis in women with HIV infection. *Cochrane Database Syst Rev* 2011 Aug 10;(8):CD008739.

16. Martinez RCR, et al. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic *L. rhamnosus* GR-1 and *L. reuteri* RC-14. *Letters Applied Microbiol* 2009;48:269-274.

Omega-3s and Brain Aging: A Connection?

ABSTRACT AND COMMENTARY

By David Kiefer, MD

Synopsis: *The researchers behind this study attempted to correlate quantitative measurements of omega-3 levels in red blood cells (RBC) with a variety of cognitive measures and tests for dementia. They found that people with lower RBC omega-3 levels had significantly worse results in brain testing.*

Source: Tan ZS, et al. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. *Neurology* 2012;78:658-664.

This new analysis of the well-known Framingham cohort (1575 community dwellers, aged 67 ± 9 years, free of stroke and dementia) attempted to improve on prior studies showing mixed results for a connection between omega-3 intake (usually fatty fish) and dementia risk. By incorporating RBC fatty acid composition (with a lifespan of 120 days), rather than just dietary recall (known to be an inaccurate reflection of blood fatty acids) or plasma omega-3 levels (which only reflect a few days' intake), the researchers were hoping to more definitively assess this connection.

The participants in this study had blood drawn and analyzed for RBC fatty acid composition, and had a brain MRI (many measurements recorded) and neuropsychiatric (NP) testing approximately three months later. The three NP testing subsets that were a part of this study focused on cognitive domains that correlate with increased risk of Alzheimer's disease: the verbal memory component of the Logical Memory test, the visuospatial memory component of the Visual Reproductions test, and the Similarities test for abstract reasoning skills.

The RBC fatty acid testing yielded multiple fatty acid results, but the researchers focused on just the two that have been shown to correlate with the risk of dementia, RBC docosahexaenoic acid (DHA) and the omega-3 index (RBC DHA and eicosapentaenoic acid [EPA] expressed as a weight percentage of the total fatty acids).

When RBC DHA levels and omega-3 index were compared to the brain MRI findings, no linear correlation was seen. However, the lowest quartile of DHA levels and omega-3 index correlated with a lower total cerebral brain volume when compared to the upper three quartiles; the authors claim that this loss of brain volume correlates with an additional two years of brain aging. Other brain MRI findings were insignificant between the quartiles for both RBC DHA and omega-3 index.

With respect to NP testing, a positive association was seen between omega-3 index and RBC DHA levels on all tests except verbal memory. Some attenuation of the relationship between the omega-3 parameters and visual memory and executive function was seen when factoring in other know risk factors for dementia and cognitive decline.

Of note, given that this was a cross-sectional study, the authors point out that it was not possible to examine this

Summary Points

- The neurological effects of omega-3 fatty acids fit with the known high concentrations of phospholipids in the central nervous system; in particular, DHA is abundant in the brain.
- Low serum DHA levels may be associated with a number of neuropsychiatric disorders.
- Although results of the study by Tan et al lend some hope to what might help prevent the development of dementia or cognitive decline, they remain preliminary and leave unanswered a few important questions.

cohort for the *development* of dementia, rather just look for connections between the omega-3 parameters and *risk* for dementia.

■ COMMENTARY

This paper is an interesting addition to the literature exploring a connection between omega-3 status and brain health. The neurological effects of omega-3 fatty acids fit with the known high concentrations of phospholipids in the central nervous system; in particular, DHA is abundant in the brain. Recent research has demonstrated, in some but not all clinical trials, a relationship between maternal supplementation and childhood neurological development.[1] One compelling and media-friendly result showed that increasing maternal DHA intake by 100 mg daily could lead to an improvement in a child's IQ of 0.13.[2] In addition, low serum DHA levels may be associated with any number of neuropsychiatric disorders.[3]

On the other end of the human lifespan, some studies have shown that omega-3 supplementation may improve cognitive function, and that lower dietary intake of omega-3 fatty acids can lead to increased cognitive decline in the elderly. However, as hinted at above, there have been pitfalls in the dietary intake research. The study being reviewed here is an interesting approach to quantifying and improving on the omega-3 intake research and cognitive changes in a late-middle age cohort by measuring RBC omega-3 levels. RBCs don't cheat on dietary recall so this research approach should lead to more accurate results.

As much as the results of the study lend some hope to what might help prevent the development of dementia or, more generally, cognitive decline in this demographic, they remain preliminary and leave unanswered a few important questions. For example, why did some of the NP

Table 1. Approximate eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) content in fish and amount of fish required to provide 1 g EPA + DHA

Type of fish	EPA + DHA content, g per 3 oz serving of fish (edible portion)	Amount of fish (oz) required to provide approximately 1 g of EPA + DHA per day*
Catfish		
Farmed	0.15	20.0
Wild	0.20	15.0
Crab, Alaskan King	0.35	8.5
Flounder/Sole	0.42	7.0
Haddock	0.20	15.0
Halibut	0.40-1.00	3.0-7.5
Herring		
Atlantic	1.71	2.0
Pacific	1.81	1.5
Mackerel	0.34-1.57	2.0-8.5
Salmon		
Atlantic, farmed	1.09-1.83	1.5-2.5
Atlantic, wild	0.90-1.56	2.0-3.5
Chinook	1.48	2.0
Sockeye	0.68	4.5
Sardines	0.98-1.7	2.0-3.0
Shrimp, mixed species	0.27	11.0
Tuna		
Fresh	0.24-1.28	2.5-12.0
White, canned in water, drained	0.73	4.0

* The intakes of fish given are rough estimates because oil content can vary markedly (> 300%) with species, season, diet, and packaging and cooking methods.

Adapted from Kris-Ehterton PM, et al. American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2753.

Table 2. Sources of omega-3 fatty acids

- Cold water, fatty fish
- Cold-expeller-pressed canoloa oil
- Ground flaxseed
- Walnuts
- Unprocessed soy products
- Fortified eggs

results correlate with RBC omega-3s, while other tests did not? How do the different RBC omega-3 levels relate to particular omega-3 intake (either dietary or supplementation), so as to make these results more clinically applicable? And, would these same results apply to non-Caucasian populations? Hopefully, follow-up research will address these questions and more in the process of refining our knowledge about omega-3s and the brain. ■

References

1. Isaacs EB, et al. 10-year cognition in preterms after random assignment to fatty acid supplementation in infancy. *Pediatrics* 2011;128:e890-898.
2. Cohen JT, et al. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. *Am J Prev Med* 2005;29:366-374.
3. Schuchardt JP, et al. Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *Eur J Pediatr* 2010;169:149-164.

No CoQ 4 U? CoQ10 and Hypertension

ABSTRACT & COMMENTARY

By Russell Greenfield, MD

Synopsis: *Results from this small intervention trial out of New Zealand strongly suggest that 200 mg/d of CoQ10 does not lower blood pressure in patients with metabolic syndrome and unsuccessfully treated hypertension.*

Source: Young JM, et al. A randomized double-blind, placebo-controlled crossover study of coenzyme Q10 therapy in hypertensive patients with metabolic syndrome. *Am J Hypertens* 2012;25:261-270.

Coenzyme Q10 (CoQ10) is considered an antioxidant with potential cardiovascular health benefits, especially in the setting of mild heart failure. A number of experts have also touted CoQ10 as a means of helping to control high blood pressure. The authors of this double-blind, placebo-controlled, 12-week crossover trial were interested in finding out whether CoQ10 would lower blood pressure (BP) in individuals previously diagnosed with metabolic syndrome and with poorly controlled BP despite active treatment with anti-hypertensive medication.

Subjects were recruited from general practitioners, research databases, and through advertisements in Christchurch, New Zealand. A total of 60 people were screened for entry, of which 31 (comprising the total number of hypertensive patients with metabolic syndrome in New Zealand — kidding!) aged 25-75 years with hypertension (defined as average clinic SBP of $\geq$ 140 mm Hg, or $\geq$ 130 mm Hg for patients with type 2 diabetes) whose BP medication had not been changed over the prior month were enrolled. Almost all subjects were Caucasian (10% Maori). Exclusion criteria included uncontrolled hypertension (office BP > 160/100 mm Hg), type 1 diabetes, type 2 diabetes requiring insulin, hemoglobin A1c > 9%, BMI > 40 kg/m^2 or an upper arm circumference > 42 cm, current smoking, warfarin treatment, or antioxidant vitamin supplementation, including CoQ10. Cardiovascular medications were not changed during the study period, and participants were asked to maintain their usual dietary and exercise practices.

Subjects were randomized to receive either CoQ10 100 mg twice daily or placebo for 12 weeks, followed by a 4-week washout period, and then received the alternative intervention for an additional 12 weeks. Participants and investigators were blinded to treatment allocation. Clinic and 24-h ambulatory BP measurements (determined at 20-minute intervals) were taken at baseline and at the end of both treatment periods. Blood for total CoQ10 levels, as well as other tests including cholesterol levels and CRP, was obtained. Primary outcome of interest was 12-week change in mean 24-h ambulatory SBP and DBP. Numerous secondary outcomes were followed and included 12-week change in 24-h mean arterial pressure (MAP), minimum and maximum BP and heart rate levels, morning surge and nocturnal fall in SBP and DBP, heart rate variability, clinic BP and heart rate, and plasma CoQ10 levels. For post-hoc subgroup analyses, the influence of potential mitigating factors including the presence of type 2 diabetes, cardiovascular disease, baseline ambulatory SBP and DBP levels, nocturnal BP dippers, treatment with specific medications including statins, metformin, and β-blockers, and attained levels of coenzyme Q10 were examined for primary and secondary outcomes.

Summary Points

- Older studies of CoQ10 for cardiovascular disease, especially NYHA Class II-III heart failure, have suggested significant clinical improvement in patients treated with CoQ10.
- The study by Young et al found no significant differences in the 24-hour average real variability for SBP/DBP or heart rate during CoQ10 vs placebo treatment. In the post-hoc subgroup analyses, there was no evidence of a treatment effect of CoQ10 on 24-h ambulatory blood pressure parameters or heart rate when compared with placebo.
- At this time, CoQ10 should not be routinely considered in the management of people with high blood pressure and the metabolic syndrome.

There were no between group differences in baseline plasma CoQ10 levels before treatment ($P = 0.18$); plasma levels increased 3.7-fold after 12 weeks of therapy ($P < 0.0001$). However, no significant reductions were identified in mean 24-h SBP/DBP, 24-h pulse pressure, MAP, or heart rate following CoQ10 therapy compared with placebo. Similarly, no changes in mean clinic SBP/DBP after CoQ10 therapy were seen versus placebo. In addition, no significant effects occurred as a result of CoQ10 administration on mean daytime or nighttime BP (a small increase in daytime DBP occurred with placebo, $P = 0.14$), daytime or nighttime heart rate (though nighttime heart rate did increase significantly with placebo compared with CoQ10, $P = 0.006$), minimum and maximum day/nighttime BP readings (but there was an increase in minimum nighttime heart rate during placebo phase compared with CoQ10 phase of 2.7 vs. -0.4 beats/min, $P < 0.05$). A significant increase in clinic heart rate with placebo treatment was identified ($P = 0.04$). There were no significant differences in the 24-h average real variability for SBP/DBP or heart rate during CoQ10 vs placebo treatment. In the post-hoc subgroup analyses, there was no evidence of a treatment effect of CoQ10 on 24-h ambulatory BP parameters or heart rate when compared with placebo.

Compliance with the interventions was very high (> 95%), and CoQ10 was well tolerated with no serious adverse events being reported. The researchers concluded that CoQ10 in a daily dose of 200 mg should not be used as a complement to conventional antihypertensive therapy in patients with metabolic syndrome and inadequately controlled hypertension due to lack of effect.

■ COMMENTARY

CoQ10 has been studied in-depth since the 1960s, and the accumulated data surrounding this antioxidant compound, also called ubiquinol for its seemingly universal presence in all cells of the body, is impressive if not always convincing. The majority of research involving CoQ10 has focused on cardiovascular disease, especially NYHA Class II-III heart failure where older studies, before the advent of a number of therapeutically effective heart medications currently in use, suggested significant clinical improvement in patients treated with CoQ10. A smattering of studies have also explored its use as a preventive against headaches, in the setting of breast cancer, as a means of enhancing gingival health and minimizing risk for statin-associated myopathy, and as a mild hypotensive agent. This latter area was the focus for the authors of the present study, and for good reasons — existing data suggest low circulating levels of CoQ10 in the setting of hypertension (data referenced in article); CoQ10 appears to be safe and well tolerated when taken for long periods of time; it may lessen oxidative stress in the body (an issue for many patients including those with metabolic syndrome and hypertension); and administration has been associated with mild reductions in both SBP and DBP in some studies. Still, many have questioned the veracity of the conclusions drawn from some studies due to significant methodological shortcomings. In general, most experts feel there is promise but a defined benefit of CoQ10 on blood pressure is far from agreed upon.

The current study was well done and of adequate duration to identify an intervention effect. The CoQ10 product and dose employed were both good choices based on prior research, and the patient population was clearly in need of additional treatment (type and number of medications used detailed in paper). And yet, no significant therapeutic benefit was identified with CoQ10 administration. Is this result the death knell for CoQ10 as a treatment option for high blood pressure?

Not yet. Remember, prior studies have shown a mild blood pressure lowering effect from CoQ10, some of which included patients with very high BP, and there are always holes to poke in studies, including this one, though they are relatively few in number. The most glaring, small sample size, weakens any conclusions; compliance was measured by pill counts; and exclusion criteria would easily knock out many patients attending a primary care clinic.

People often stop taking their medications due to perceived side effects, a fact especially true in the setting of hypertension. Safe, effective options that are easy to take are highly desirable. Promising results from early studies with CoQ10 suggested it might be a part of the solution,

but the current small yet well-done study does not support that conclusion. It is safe to say that CoQ10 should not be routinely considered in the complex management of people with inadequately treated high BP and the metabolic syndrome, the combination being a notoriously challenging clinical situation of increasing incidence, but these results also should not be interpreted as the final chapter regarding CoQ10's effectiveness as an adjunct in the management of hypertension in all circumstances. ■

Summary Points

- Tai Chi Chuan is an Asian exercise regime involving slow movements and breathing control.
- Tai Chi Chuan may have some beneficial effects on cardiac health, but the evidence to date is limited.
- Measuring numerous outcomes is not necessarily a more reliable way to identify effective interventions.

Study of Tai Chi Chuan for Cardiovascular Disease Provides Little Guidance

ABSTRACT & COMMENTARY

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Dr. O'Mathúna reports no financial relationships relevant to this field of study.

Synopsis: *A prospective before and after study examined the impact of Yang-style Tai Chi Chuan on cardiac parameters. Significant improvements were found for fasting glucose, blood pressure, and body weight. A subgroup analysis found that those who engaged in 80% or more of the sessions had some improvement in cardiovascular parameters. However, limitations in the study design and reporting weakened the strength of any recommendations based on the study's findings.*

Source: Huang Y-T, et al. Adhering to a Tai Chi Chuan exercise program improves vascular resistance and cardiac function. *Int J Gerontolog* 2011;5:150-154.

TAI CHI CHUAN IS AN ANCIENT ASIAN FORM OF EXERCISE AND relaxation. A number of different types of Tai Chi Chuan are practiced, but there is insufficient evidence to determine if the styles have clinical relevance. The most popular form is the Yang style, which was used in this study. Participants slowly go through a series of movements while controlling their breathing. Although the movements are relatively slow, Tai Chi has been classified as a moderately intense form of aerobic exercise. For this reason, and because of its low intensity, it has been recommended for older people.

Previous research suggested that Tai Chi may have beneficial effects on cardiovascular disease.[1] The study reported here evaluated the effect of Tai Chi on markers of cardiac function and was conducted in Taipei, Taiwan. Participants were recruited from a Tai Chi club at a hospital in the city. All subjects exercised at least three times per week prior to the study, but the report did not state what form of exercise they undertook. Participants were free from cardiovascular disease, hypertension, hyperlipidemia, diabetes or other serious disease. None of the subjects was overweight (mean body mass index 23.4 kg/m^2), 70% were female, and the mean age was 62.3 years.

The report stated that 122 subjects were recruited and 83 completed pre- and post-test measurements. All subjects participated in a Yang style Tai Chi program consisting of 24 movements carried out over 1 hour. Subjects practiced Tai Chi three times a week for 5 months. No control group was involved. Analyses were conducted on the 83 subjects who completed the measurements.

Outcomes were measured before and after the 5-month program. Blood analyses were conducted to measure fasting glucose, total cholesterol, LDL-cholesterol, triglyceride, C-reactive protein, and uric acid levels. Vascular resistance and vascular compliance were measured with a Dynapulse 200 M monitor (which uses a noninvasive cuff to measure arterial pulsation signals; details are published elsewhere.[2]).

After 5 months of Tai Chi, significant reductions (all $P < 0.01$) were found in body weight (0.6 kg), systolic (8 mm Hg) and diastolic blood pressure (6 mm Hg), and fasting glucose (4.7 mg/dL). No significant changes were found for pulse pressure, heart rate, or other biochemistry levels. Of the 12 cardiovascular parameters measured by the Dynapulse monitor, only systemic vascular resistance (SVR) was significantly lowered.

The data from the study were further analyzed according to two subgroups: an adherent group (who attended more than 80% of the Tai Chi sessions) and a non-adherent group (attended ≤ 80%). It was not mentioned if this subgroup analysis was planned prior to the study. The

adherent group contained 33 subjects with 34 in the non-adherent group. No explanation was provided regarding why the two groups contained 16 fewer subjects than the total who completed the study.

The two subgroups did not differ significantly at baseline. After the 5-month Tai Chi program, the adherent group had significantly lower triglyceride levels than the non-adherent group. No other biochemistry levels differed significantly. Regarding cardiovascular parameters, the adherent group had significantly more improvement in left ventricular contractility, cardiac output, cardiac index, stroke volume, and SVR (all $P < 0.01$). The non-adherent group had significantly better brachial artery compliance ($P = 0.02$).

The authors acknowledged that their study had limitations; a relatively small number of subjects was involved, and only indirect measures of cardiac performance were measured. The subjects were already involved in a Tai Chi club and may have been engaged in other health-promoting activities compared to the general population. The reasons for non-adherence were not explored. Other confounding factors were not examined. They concluded that "longitudinal studies over several years are required to determine the effects of TCC [Tai Chi Chuan] on these clinically important outcomes."

■ COMMENTARY

This study is of limited value in evaluating the effectiveness of Tai Chi on cardiovascular disease. The lack of a comparison group means that confounding factors cannot be ruled out as contributory factors to any changes. No power analysis was reported to demonstrate how many subjects were needed in the study. The report did not discuss the factors contributing to the changing numbers of subjects in the various stages of analysis: why 122 subjects were recruited, complete data were reported for 83 subjects, and then only 67 subjects were included in the subgroup analysis.

Another limitation not discussed in the report was the contribution of multiple hypothesis testing.[3] When statistical significance is set at $P = 0.05$, there is a 1 in 20 chance of getting a false positive. The chance of obtaining a false positive result increases with each additional outcome tested. For example, with five outcomes, the calculated chance of a false positive is almost 1 in 4.3 The study measured numerous outcomes without a priori selection of primary and secondary outcomes. A statistical test (like the Bonferonni Correction) should have been conducted to take account of the problems with multiple hypothesis testing. In addition, it was not clear if the subgroup analysis was planned prior to conducting the study, or if it was developed after the initial analysis including all subjects revealed few significant improvements.

Overall, the design of the study without a control group introduced serious limitations in its attempt to evaluate the effectiveness of Tai Chi. The use of multiple outcome measures and the sub-group analysis introduced further limitations. A number of important factors were not described in the article reporting the study.

A systematic review was previously conducted of Tai Chi for patients with cardiovascular disease or risk factors for cardiovascular disease.[1] This review included many studies published in Chinese which previously had not been examined in English reviews. The review found some evidence of benefit, but concluded that the literature was limited. Given this, the reviewers concluded that Tai Chi may be a reasonable adjunct to conventional care, especially for those who are unwilling or unable to engage in other forms of physical activity. However, more rigorous research is needed to provide clearer evidence of its effectiveness. ■

References

1. Yeh GY, et al. Tai chi exercise for patients with cardiovascular conditions and risk factors: a systematic review. *J Cardiopulm Rehabil Prev* 2009;29:152-160.
2. Brinton TJ, et al. Development and validation of a noninvasive method to determine arterial pressure and vascular compliance. *Am J Cardiol* 1997;80:323-330.
3. O'Mathúna DP, et al. Critically appraising quantitative evidence. In: *Evidence-Based Practice in Nursing and Healthcare: A Guide to Best Practice*, 2nd ed. Ed. Melnyk B, Fineout-Overholt E. Philadelphia: Lippincott Williams & Wilkins, 2010; 81-134.

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 Instructions

To earn credit for this activity, follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. Like women with bacterial vaginosis, it has been clearly shown that women with VVC have a decrease in vaginal H2O2-producing *Lactobacilli* spp.

a. True

b. False

2. Although most clinical studies studying probiotics for VVC have administered them intravaginally, which of the following strains has been shown to be potentially efficacious when used orally?

a. *Lactobacillus salivarius* LS114

b. *L. rhamnosus* GR-1 and *L. reuteri* RC-14

c. *L. acidophilius*

d. *L. catenaforme* LC-203

3. Two recent studies indicate that aspirin does which of the following?

a. Confers a modest reduction in the risk of cancer and cancer death

b. Prevents the local spread of cancer but not distant metastasis

c. Has little impact on non-reproductive cancers

d. Acts to prevent cancer death but not cancer incidence

4. Which of the following is true regarding the findings in the Tan et al (2012) study regarding omega-3s and brain health?

a. People with lower RBC DHA have significantly larger total cerebral brain volume.

b. Increased fish intake leads to less dementia.

c. Positive associations were seen between omega-3 values and all NP tests except verbal memory scores.

d. The demographic studied were people with a prior stroke and between the ages of 40-50 years old

5. Tai Chi Chuan is an Asian practice that can be described as:

a. A non-invasive way of administering acupuncture.

b. A form of moderate exercise involving slow movements.

c. A challenging and intense form of rigorous exercise.

d. An exercise regimen performed in a stationary position.

In Future Issues:

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