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INSIDE

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Melatonin for Menopausal Sleep Disorders and Quality of Life

By Judith L. Balk, MD

Dr. Balk is Associate Professor, Magee-Women's Hospital, University of Pittsburgh; she reports no financial relationship to this field of study.

SLEEP DISRUPTION IN MENOPAUSE IS COMMON. ONE-FOURTH TO ONE-half of all women will note some sleep complaint during menopause, as compared to approximately 15% in the general population.[1] Menopausal women are 3.4 times more likely to report trouble sleeping than premenopausal women, although there have been few documented polysomnographic changes associated with menopause.[1] Aging itself appears to be a risk factor for changes in sleep studies. Three types of sleep disorders are associated with menopause: insomnia with depression, sleep-disordered breathing, and fibromyalgia.[1] In addition, perimenopausal and postmenopausal women often have vasomotor symptoms contributing to disrupted sleep. A "domino hypothesis" has been proposed, in which vasomotor symptoms lead to disrupted sleep, which then leads to insomnia followed by depression.[1] Clearly, intervening at an early stage in this "domino" scenario might be helpful in preventing insomnia-related depression.

The changing hormonal milieu in menopause may have direct effects on various components of sleep architecture.[1] For instance, estrogen administration decreases sleep latency and the number of cyclic spontaneous arousals, and when women are in the lower estrogen phases of the menstrual cycle, the number of sleep arousals doubles. Progesterone appears to have two direct effects on sleep; the first is that progesterone is considered to be sedating because it is a GABA agonist; the second effect of progesterone is that it is a respiratory stimulant and has been used to treat mild obstructive sleep apnea.[2] Thus, progesterone that is produced in the luteal phase may be protecting against sleep apnea; sleep apnea is more common postmenopausally, when no progesterone is produced by the ovary, than premenopausally. Cortisol and testosterone also may play a role in sleep architecture.

Melatonin

In addition to gonadal and adrenal hormones, melatonin also may play a role in sleep architecture in menopausal women.

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Melatonin secretion throughout the diurnal cycle is higher in younger people than in older adults.[3] In addition, while melatonin overall decreases with age, there appear to be two specific and dramatic periods of reduction in melatonin levels in women: from age < 40 to 40-44 years of age, and from 50-54 to 55-59 years of age.[4] Because melatonin levels appear to decrease prior to the onset of menopause, some investigators have suggested that melatonin may be linked to the initiation of menopause.[4] The interactions between melatonin and estrogen are complicated. It is likely that changes in melatonin secretion affect sex steroids, but the converse probably does not occur.[5] Postmenopausal women with insomnia generally have lower melatonin levels than postmenopausal women without insomnia. In addition, depressed patients have lower levels of melatonin compared with normal controls.[6]

The amino acid L-tryptophan is converted to serotonin and then to melatonin in the pineal gland.[7] Melatonin synthesis follows a circadian rhythm, in which little melatonin is secreted during daylight hours. With the onset of darkness, melatonin synthesis and release begin. Melatonin levels peak between 2 a.m. and 4 a.m. Darkness is stimulatory and light is inhibitory to melatonin synthesis and release.[5] Day-night light cycles modify the melatonin rhythm, and brief pulses of light of sufficient intensity and duration abruptly suppress melatonin production.[5] Melatonin receptors exist in the brain and in peripheral tissues, such as the gut and ovaries, and blood vessels; melatonin likely has circadian rhythm, reproductive, and temperature regulation functions. In addition to receptor-mediated actions, it also has nonreceptor actions, such as being a potent scavenger of oxygen-centered free radicals and augmenting the immune response. Melatonin has been shown to regulate progesterone production via melatonin receptors in human granulosa-lutein cells.[8] Melatonin's effects on perimenopausal symptoms may be related to a direct action of melatonin on the central nervous system, as opposed to the sex hormone pathway.[9] Melatonin may play a role in inhibiting breast cancer, although evidence for this is indirect.[5] Interestingly, melatonin can react with the GABA receptor in a benzodiazepine-like way.[7] Rohr and Herold suggest that this interaction may help to explain melatonin's effects on mood improvement and pain reduction in fibromyalgia patients. Gabapentin, a GABA analogue, is used to treat menopausal hot flushes;[10] it is possible that melatonin, via GABA-like effects, may be beneficial for perimenopausal and menopausal women.

Animal Research

Gonadal and adrenal hormones may act on different sites in the pineal gland and thus may affect melatonin in different ways.[11] Both progesterone and estrogen receptors exist in the pineal gland in animals. In rats, melatonin synthesis and secretion is reduced during proestrus, when estradiol and progesterone levels are elevated. Antiestrogens reduce the nocturnal peak, whereas antiprogestogens increase it. In some animals, the secretion of melatonin from the pineal gland plays a major role in regulating reproductive physiology; in humans, these relationships are less clear.[12]

Human Research

A blinded clinical trial in Italy investigated 6 months of placebo or melatonin, 3 mg, in premenopausal, perimenopausal, and postmenopausal women with neurovegetative, sleep, and/or psychological symptoms.[13] Randomization was not stated, nor was assignment allocation. The investigators noted that at 6 months, the placebo and melatonin groups differed in mood; 6.7% of melatonin-treated subjects reported continuing morning depression, compared to 21% of placebo-treated subjects ($P < 0.05$). The investigators also noted that 12 menopausal women (at 1 and 2 years after total cessation of menses) reported a reacquisition of normal menstrual cycles. The ages of these women were not stated. The investigators note that melatonin depressed the production of follicle stimulating hormone only in women with low melatonin levels at baseline. They postulate that melatonin "restores menstrual cyclicity and fertility in perimenopausal or menopausal women." More research must be done to fully investigate the hormonal effects of melatonin. Although not statistically significant, many women reported a tendency to amelioration of hot flushes and improvement in quality and duration of sleep.

Researchers in Pittsburgh conducted a pilot double-

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blind, placebo-controlled study in which perimenopausal women were randomized to melatonin (3 mg orally nightly) or placebo in a 3:1 ratio, results of which were presented in abstract form at Women's Health 2011: The 19th Annual Congress.[14] Outcomes included Menopausal Quality of Life, sleep, and menstrual patterns, and results showed that melatonin significantly improved physical aspects of quality of life as measured by the Menopause-specific Quality of Life Questionnaire. Also, subjects in the melatonin group had significantly fewer menstrual periods over the 6-month study. Sleep quality did not differ significantly between groups, although subjects in the melatonin group thought that they were sleeping better and feeling better. Because melatonin is thought to directly increase progesterone production,[8] improved sleep and fewer menstrual cycles would be biologically plausible.

One large study investigated a "prolonged-release melatonin formulation," in a dose of 2 mg.[15] This medication was approved in Europe in 2007 for treatment of primary insomnia in patients ages 55 or older (limit was based on the known decrease in melatonin levels with age). A randomized, double-blind, parallel-group, placebo-controlled trial was conducted over roughly 30 weeks in 930 men and women aged 18-80 with primary insomnia. Two-thirds of the patients were female. Sleep latency was improved in the treatment group relative to placebo in those aged 55-80, but not in the whole group, which included younger patients. Other sleep, quality of life, and clinical status variables improved in the treatment group relative to placebo. No signs of tolerance were seen, and no withdrawal symptoms or rebound insomnia were detected. One patient in the melatonin group experienced palpitations, and this was assessed as possibly drug-related. Otherwise, the only adverse event that was deemed treatment-related was in a subject treated with placebo.

Safety

Theoretically, melatonin may have interactions with medications, botanicals, and supplements with antiplatelet/anticoagulant constituents and might increase the risk of bleeding in some people. For instance, there have been several case reports of excessive bleeding in patients taking warfarin and melatonin.[16] Concomitant use with medications or botanicals that have sedative properties might enhance both the therapeutic and adverse effects of melatonin. When melatonin is administered in the morning, dizziness, drowsiness, and lack of alertness during the day have been reported.[7] Based on the evidence, it is not clear if higher dosages have more side effects.

Conclusion

More research is necessary to fully delineate the indications for melatonin in perimenopausal and postmenopausal women. It may help with sleep issues, but evidence for this is limited. Short-term usage of melatonin is a rational therapeutic approach for the alleviation of insomnia and circadian phase disorders of peri- and postmenopausal women, as these periods of life are characterized by changes in sleep quality and circadian rhythms.[5] The best effect of melatonin is shown when it is administered 6 hours before the natural peak[7] that occurs between 2 a.m. and 4 a.m. Thus, administering melatonin between 8 p.m. and 10 p.m. would give the best results for sleep disorders. Dosages above 5 mg do not appear to be better than dosages between 0.5 mg and 5 mg.

Recommendation

Melatonin at dosages up to 5 mg may be helpful for perimenopausal and postmenopausal women with sleep disorders, although more research is necessary to delineate the indications, length of treatment, and dosage. Melatonin appears to be safe in most individuals, but more research is necessary to fully understand its side effect profile and contraindications. ■

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Systematic Review of Energy Healing for Cancer Provides Little Concrete Guidance

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing, Dublin City University, Ireland; he reports no financial relationship to this field of study.

Synopsis: *This systematic review searched for studies using any methodology that measured outcomes in cancer patients who received energy healing techniques. Some evidence of improvements in psychosocial outcomes was found, but the methodological deficiencies in the original studies undermined confidence in their findings. The reviewers call for further research studies designed according to high-quality research standards.*

Source: Agdal R, et al. Energy healing for cancer: A critical review. *Forsch Komplementmed* 2011;18:146-154.

This article describes a systematic review of the efficacy and effectiveness of various "energy healing" therapies used for cancer patients. Complementary and alternative medicine (CAM) commonly uses the term "energy healing" and applies it to a wide variety of therapies. The therapies examined in this systematic review were Reiki, therapeutic touch (TT), and healing touch.

An extensive search was conducted of the medical and psychological literature from 1998 to 2010. The inclusion and exclusion criteria were clearly described. The reviewers identified 147 articles in PubMed, with no additional studies located in the other databases searched. All but eight of these articles were excluded with explanations given. Of these, six were quantitative studies and two were qualitative studies of the efficacy and effectiveness of energy healing for cancer patients.

All eight studies were summarized in tables and discussed in narrative format. A meta-analysis was not possible because different energy therapies were employed, and even when the same outcomes were measured, different tools were used. The studies used a wide variety of methodologies, primarily focused on relieving symptoms such as pain, fatigue, depression, anxiety, or nausea. Six studies measured pain outcomes, with three reporting significant relief after receiving energy healing (P = 0.03, 0.002, and 0.0001, respectively). Two of these were randomized controlled trials. The third was intended to be randomized, but patients refused assignment to standard care and the trial was stopped after accruing one-fourth of the patients planned. Two other studies reported no significant changes in pain, and a qualitative study found that people reported reduced pain after TT. Overall, the reduction in pain was roughly 1 on a 10-point visual analogue scale (VAS). This finding is in keeping with a reduction of 0.83 (95% confidence interval -1.16 to -0.50) on a 10-point VAS found in another meta-analysis of touch therapies for pain.[1]

One study found that fatigue decreased significantly while another found only a non-significant reduction. Studies that measured nausea found no changes. Use of pain medication and other measures such as heart rate and blood pressure did not change significantly. In qualitative interviews, people reported improved feelings of well-being after energy therapies, but quantitative measurements found varying outcomes.

The reviewers assessed the methodological quality of the studies using the SIGN quality scale (Scottish Intercollegiate Guidelines Network).[2] None of the studies included in the review met the criteria for high standards that would produce reliable results. Three studies achieved an overall positive rating, meaning that they met some of the criteria expected of high-quality studies, implying that the conclusions would be unlikely to change if the remaining quality standards had been achieved. The other five studies had overall negative ratings, meaning that few or none of the methodological standards were attained. Therefore, the conclusions would likely or very likely change if the methodology employed was improved upon.

Study weaknesses centered around numbers of subjects, blinding, and conflation of roles of healer and researcher. A total of 531 subjects were involved in the eight trials, with individual trials involving from 7 to 230 participants. Only one study reported adequate blinding. Another study began as a single-blind trial, but the healer unblinded himself during the trial (and quit his role). The trial ended up as a descriptive study. In at least three studies the investigator was also the healer, raising concerns about potential bias.

In spite of poor study quality, the reviewers note that the results are interesting enough to warrant further research. Future studies should strive to use high-quality

research standards. The energy modalities used are complex and raise challenges for researchers; however, some of the studies reviewed demonstrate that rigorous research methodologies are possible with energy therapies.

The authors concluded that few studies have examined the effects of energy healing in cancer patients "and none of them are of a size or quality that allows reliable conclusions to be drawn."

■ **COMMENTARY**

This systematic review was conducted well in many regards. The search strategy was described in detail, using many relevant terms, but the term "energy" was not used. This omission was not explained, although it likely would have led to numerous articles addressing more conventional understandings of energy. The authors searched from 1998 forward without explaining why this date was chosen. At least one study of Reiki in cancer was missed because of this.[3] Although a number of electronic databases were searched, specific CAM databases were not used such as that within the Cochrane Library. The fact that no additional studies were found in databases other than PubMed would suggest that their choice of databases was not optimal. They also restricted their search to peer-reviewed literature. This would be expected to identify higher quality studies, but they may have missed some suitable studies. On the other hand, no restrictions were placed on the study methodologies which ensured that a broad range of studies were included. Both qualitative and quantitative studies were reviewed. The most consistently measured outcome was pain level. While some trials reported significant pain reduction, the effect size was modest.

Energy healing therapies like TT have been studied in controlled trials since the 1970s. This review demonstrates that their methodological quality continues to be a significant problem. At the very least, interventions should be described fully so that readers can identify which therapies are being investigated. Full blinding is not possible given that the healers must know what they are doing. However, those measuring outcomes should be blinded to group allocation. This is particularly important given that these therapies are usually recommended for symptoms like pain and well-being, which are strongly influenced by the placebo effect. For these reasons, the regular use of investigators as healers is particularly problematic in these trials.

In addition, patients can be blinded in these studies by using sham therapies or waiting list controls. Such controls are challenging, though, because of disagreement over the mechanisms of energy therapies. Different proposals are made for suitable controls based on hypotheses that some non-physical energy, healers' intentions, patients' expectations, or various hand movements are central.

Currently, firm conclusions about the efficacy or effectiveness of energy healing are not supported by the research studies reviewed in this article, in spite of claims, for example, that therapies like Reiki are research-supported.[2] Until researchers adopt rigorous methods, questions will remain about the effectiveness of energy therapies, and until the results of more rigorous research are available, energy therapies should not be added to clinical practice in general. However, given their popularity, it is likely they will continue to be used by patients based on uncontrolled observation of therapeutic benefits. ■

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Mag Me? Magnesium for Hot Flashes

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *In a small 5-week pilot trial examining the use of magnesium for the treatment of hot flashes, women with a history of breast cancer experienced improvements in hot flash frequency and severity, but no significant impact on overall quality of life.*

Source: Park H, et al. A pilot phase II trial of magnesium supplements to reduce menopausal hot flashes in breast cancer patients. *Support Care Cancer* 2011;19:859-863.

Based on clinical observation in two patients that was reported in 2009[1] and further uncontrolled observations, the authors of this small pilot trial sought to explore the potential benefits of magnesium supplementation in women with a history of breast cancer who were experiencing hot flashes.

A total of 31 subjects with bothersome hot flashes (defined as occurring 14 or more times a week for at least a month, and being of sufficient severity that treatment was desired) after breast cancer treatment were enrolled. All subjects had normal renal function, no recent change in dose of tamoxifen, raloxifene, or aromatase inhibitors, and were rated to have good performance status.

Baseline data were collected during the first week of the trial when magnesium was not administered. Over the

following 2 weeks participants were provided with magnesium oxide 400 mg (250 mg elemental magnesium per tablet) to be taken at bedtime; if symptoms decreased adequately, they were instructed to remain on the same dose throughout the remainder of the trial (2 more weeks). If, however, bothersome symptoms persisted, subjects were permitted to double the dose to 400 mg twice daily (500 mg of elemental magnesium). A pill count was completed at the end of the study.

Subjects were asked to maintain a prospective hot flash diary over the 5-week period and to complete a number of questionnaires designed to 1) assess severity and frequency of hot flashes, and 2) assess change in measures of quality of life. The primary question to be resolved was whether oral magnesium supplementation would decrease the frequency and severity of hot flashes (the hot flash score) by 50%, a level deemed clinically significant by the researchers. Secondary outcomes of interest were the effects of magnesium on quality of life and side effects or toxicities.

Only 29/31 subjects actually received the magnesium supplements (average age 54 years, 24 postmenopausal [15 reported duration of hot flashes for > 18 months], 6 African Americans; 8 on tamoxifen, 9 on aromatase inhibitors, 14 on antidepressants), and 25/29 completed the full study. One subject was lost to follow-up and three others discontinued treatment (two due to possible side effects) before any assessments of impact on hot flashes had been performed. All survey forms were completed and returned. Compliance was reportedly very high, with all but three subjects taking all their pills (the three took 70% of their magnesium supplements). A total of 17 participants increased the dose of magnesium to 800 mg daily after 2 weeks.

Results were promising — both hot flash frequency and score were significantly reduced, with 56% experiencing a > 50% reduction in hot flash score and 76% a > 25% reduction at the end of 4 weeks compared with baseline. Average weekly hot flash frequency decreased by 41% ($P = 0.009$) by week 5, and average weekly hot flash score decreased by 50% ($P = 0.02$). However, magnesium supplementation had no significant effect on overall quality of life or degree of sleep disturbance, but significant improvements in fatigue, perceived distress level due to hot flashes, and severity of abnormal sweating was noted.

The authors conclude that oral magnesium supplementation is effective in reducing the severity and frequency of hot flashes in women after treatment for breast cancer.

■ COMMENTARY

Hot flashes can be one of the most troubling symptoms experienced by women during perimenopause. Such vasomotor symptoms also can complicate breast cancer treatment with agents such as tamoxifen and aromatase inhibitors, and not uncommonly occur during hormone therapy for the treatment of prostate cancer. In light of safety concerns associated with estrogen replacement therapy, conventional medical treatment has emphasized the use of SSRIs, SNRIs, and clonidine, all of which appear to offer benefit but at the cost of potential for significant side effects. A variety of complementary and alternative medicine therapies show promise for the treatment of hot flashes, including acupuncture and Chinese medicinal herbs, mind/body therapies such as visualization and yoga, and select supplements and Western botanicals, yet the search for safe, effective, and inexpensive interventions to relieve hot flashes continues — which is why the positive results from the present study might offer a breath of fresh, cold air to hot flash sufferers.

Magnesium is commonly administered in a variety of clinical settings, including for prevention of cardiovascular disease, and treatment of asthma and eclampsia, and has been shown to be safe in people with normal kidney function. With respect to hot flashes the mechanism of possible beneficial action is unknown, but it is acknowledged that magnesium has effects on both blood vessels and nerves, and that it may also impact serotonin levels. In general, magnesium supplementation is quite safe except in the setting of significant renal impairment. In the current study, side effects occurred in two participants — one subject experienced a migraine (which is interesting, since the mineral can be used as a preventive treatment against migraines) and one had nausea. Two subjects also developed what was termed "grade 1 diarrhea." Glycinate and gluconate forms of magnesium seem less likely to cause this disturbance in bowel habits. Supplemental magnesium is affordable (the magnesium oxide used in this trial cost $0.02 per day), and food sources of magnesium are plentiful and include leafy greens, nuts, beans, whole grains, and avocados.

It's enticing to jump on the magnesium bandwagon right away to try to help our patients with hot flashes, but it is important to keep in mind that this study focused on women with a history of breast cancer, that it was a small pilot trial with no placebo group, and that results were not parsed to determine the impact of antidepressant use. It is reasonable to assume that a beneficial impact on hot flashes also might occur in other settings, but it will be helpful to have corroborative data (the authors are planning a Phase 3 trial). That stated, there seems no harm in exploring a trial of magnesium therapy for people experiencing hot flashes provided kidney function is normal. ■

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Something's Fishy – DHA and Prostate Cancer

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *In a shocking series of findings, this well-done prospective study showed that in men older than age 55 years a higher proportion of serum omega-3 fatty acids, specifically DHA, actually may increase the risk for high-grade prostate cancer.*

Source: Brasky TM, et al. Serum phospholipid fatty acids and prostate cancer risk: Results from the Prostate Cancer Prevention Trial. *Am J Epidemiol* 2011;173:1429-1439.

DATA SUGGEST THAT THE OMEGA-3 FATTY ACIDS FOUND IN fish oils may help prevent a variety of cancers, including prostate cancer, with the most likely mechanism being modulation of inflammation. The researchers behind this prospective, nested case-control trial were interested in furthering investigation in this area, working from the hypothesis that higher serum omega-3 fats would be associated with a lessened incidence of prostate cancer, and that high serum concentrations of omega-6 and *trans* fatty acids would be tied to an increased risk.

The study comes out of the Prostate Cancer Prevention Trial, a randomized, placebo-controlled trial that evaluated the effect of finasteride on prostate cancer risk (of note, results suggested that finasteride reduced the risk of prostate cancer; however, cancers that developed in those on the medication were more aggressive). Subjects were men older than 55 years with no history of antecedent cancer (save for non-melanoma skin cancer) or severe benign prostatic hyperplasia; prostate-specific antigen concentrations of ≤ 3.0 ng/mL; and normal digital rectal examination. Nearly 19,000 men receiving care out of 221 U.S. medical centers were randomized to receive either finasteride or placebo. Over the course of the 7-year study, men underwent annual prostate-specific antigen and digital rectal examination testing. Men who had an abnormal digital rectal examination or finasteride-adjusted prostate-specific antigen result ≥ 4.0 ng/mL were recommended for prostate biopsy. At the final study visit, all men who had not been diagnosed with prostate cancer also were requested to undergo prostate biopsy. Pathology specimens were reviewed for adenocarcinoma by both the pathologist at the local study site and at a central pathology laboratory, with concordance achieved in all cases. Clinical stage was assigned locally, and grade was assigned by a single pathologist at the central laboratory. Non-fasting blood was collected 3 months prior to randomization and then annually until either the end of the study or a diagnosis of prostate cancer was made. Total lipids were extracted from serum, and phospholipids were separated from other lipids by one-dimensional thin-layer chromatography. Proportions of fatty acids were categorized into quartiles on the basis of the distribution in the controls.

Excluding men without baseline serum available for analysis, cases (n = 1809) were men with biopsy-confirmed invasive prostate cancer identified before the study was unblinded, and controls (n = 1809) were selected from subjects who had no cancer detectable at the end-of-study biopsy. Controls were frequency matched to cases on distributions of age (± 5 years), treatment group (finasteride or placebo), and other factors. All models were adjusted for the matching variables of age, family history of prostate cancer, and race, and additionally adjusted for risk factors including history of diabetes, alcohol consumption, and body mass index.

Results were sobering — proportions of DHA were *higher* among high-grade cases of prostate cancer (Gleason score 8-10) compared with controls, whereas *trans* fatty acid levels were significantly *lower* among high-grade cases compared with controls. Higher quartile levels of percent serum DHA were associated with an almost doubling of the risk for high-grade disease compared with the lowest quartile; on the other hand, a significant inverse relationship was found between the percent serum *trans* fatty acid level and risk of high-grade prostate cancer. Associations for DHA + EPA were similar to those for DHA alone. There were no other significant findings for the remaining phospholipids between control and cancer groups, including for EPA alone or linoleic acid, and no association identified for any fatty acid with low-grade disease (Gleason score 2-7).

The researchers concluded that, in this large prospective investigation of inflammation-associated phospholipid fatty acids and prostate cancer risk, omega-3 fatty acids do not reduce prostate cancer risk, and *trans* fatty acids do not increase prostate cancer risk — in fact, just the opposite. The authors are frank about being "disconcerted" by their findings, noting that the results illustrate the complexity of research on nutrition and chronic disease risk.

■ COMMENTARY

Good research has a way of turning things topsy-turvy and making us revisit long-held assumptions previously deemed fact. This paper represents good research. The study authors entered into their protocol fully expecting to find that higher serum levels of omega-3 fats would be protective against prostate cancer, and that the presence of those evil *trans* fats in high concentrations would be shown yet again to be harbingers of ill health. Oops…

A wealth of research strongly suggests that inappropriate inflammation may contribute to the development of carcinogenesis, and studies that examine dietary omega-3 fatty acid intakes have supported the general inflammation–cancer hypothesis. Simply put, omega-3s are anti-inflammatory or at least *less* pro-inflammatory (good), while omega-6s and *trans* fatty acids are *more* pro-inflammatory (bad). It's been pretty easy, pretty linear, but like few studies before, these investigators looked at things differently — actual serum levels of phospholipid fatty acids. And they found the opposite of what was anticipated — increased risk with higher proportions of DHA, lowered risk with increased proportions of *trans* fats, and no identifiable association with omega-6s or EPA. These findings, when taken together with those from the large EPIC trial that suggested an increased risk of both high- and low-grade prostate cancer in the highest quintile of DHA blood levels, as well as an increased risk of prostate cancer with increasing blood levels of EPA (unlike what is reported in the current study),[1] must give us pause when considering the overall benefits, and risks, associated with omega-3 fatty acids. The authors themselves state it is possible that omega-3 fatty acids *promote* tumorigenesis.

This was an extremely well-done bit of research, which makes the conclusions all the more concerning. The researchers even analyzed the results on the basis of whether subjects received finasteride or not (cases of high-grade prostate cancer were more likely to have been randomized to treatment with finasteride). Yes, there was over-sampling with respect to the frequency of prostate biopsy, as evidenced by the fact that almost all cases of prostate cancer detected were local stage (although high-grade disease was detected). In addition, the study authors point out that they looked at fatty acid as a proportion (%) rather than by concentrations. Regardless, across an array of statistical analyses the findings held true.

Now what? DHA is often thought of as the "eye and memory fatty acid" with its cousin, EPA, typically considered the "heart and joint fatty acid." Practitioners should discuss the risks and benefits of fish oils with individual patients based upon their unique clinical circumstances. For those using fish oil supplements for general health purposes, especially men, it may be worthwhile taking products that contain a significantly higher percentage of EPA compared to DHA. Clarity on this topic demands further data. Considering how many people make a habit of eating fatty, cold water fish for health reasons or who take fish oil supplements, here's hoping those data come soon. ■

Reference

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That Cup of Joe Affects Your Prostate Cancer Risk

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Dr. Gupta is Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV; Dr. Gupta reports no financial relationship relevant to this field of study.

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Synopsis: *Regular coffee consumption is associated with a prominent decrease in fatal or metastatic prostate cancer.*

Source: Wilson KM, et al. Coffee consumption and prostate cancer risk and progression in the health professionals follow-up study. *J Natl Cancer Inst* 2011103:876-884.

Coffee has a long history of being blamed for many ills, sometimes justly. However, emerging research indicates that it may not be so bad after all. For instance, recent studies have demonstrated that coffee may have benefits, such as protecting against Parkinson's disease, type 2 diabetes mellitus, and liver cancer.[1] In another prospective study of American men, coffee consumption was shown to prevent symptomatic gallstone disease.[2] In addition to caffeine and some of the phytochemicals, coffee also has a high content of antioxidants. This has prompted researchers to investigate the relationship of malignancies with coffee consumption. In a study looking at two large cohorts of men and women, regular consumption of decaffeinated coffee was associated with a 52% reduction in incidence of rectal cancer compared to those who never consumed decaffeinated coffee, whereas consumption of coffee or tea with caffeine or caffeine intake was not associated with the incidence of colon or rectal cancer in either cohort.[3] Similarly, in the present study, researchers attempted to investigate the relationship between coffee intake and risk of overall prostate cancer, including that of aggressive disease.

Using data from the Health Professionals Follow-up Study, Wilson et al conducted a prospective cohort study of 47,911 men followed for more than 20 years. Beginning in 1986, the study participants were followed through biennial questionnaires to update information on

lifestyle and health outcomes, and usual diet (including intake of regular and decaffeinated coffee), and were assessed every 4 years. These men, who were 40-75 years old at the start of the study, completed a questionnaire about their health and lifestyle when they enrolled. They then answered regular follow-up questionnaires to update this information. The researchers identified diagnoses of prostate cancer initially by self-reports from the men themselves or their relatives and then confirmed these by checking medical records and pathology reports. Deaths were ascertained through reports from family members and the National Death Index and the underlying cause of death was decided based on information such as medical records, registry information, and death certificates. Total prostate cancer incidence, excluding stage T1a cancers (which are discovered incidentally during treatment for benign prostatic hypertrophy), was studied. Data for men with advanced, lethal, or non-advanced cancers were examined separately to distinguish those patients in whom the cancer was likely to progress clinically.

The study participants overall consumed an average of 1.9 cups of coffee per day. During the 20 years of follow-up (from 1986 to 2006), the researchers found that 5035 of the 47,911 men were confirmed to have developed prostate cancer. Of these, 642 patients had lethal type prostate cancers (defined as fatal or metastatic), 896 were advanced, and 3,221 were non-advanced.

Researchers found that men drinking six or more cups per day had an 18% lower risk of overall prostate cancer compared with non-coffee drinkers (relative risk [RR], 0.82; 95% confidence interval [CI], 0.68-0.98). However, when only lethal forms of the prostate cancer were considered, the risk was decreased by approximately 60% vs non-coffee drinkers (RR, 0.40; 95% CI, 0.22-0.75).

Additionally, both caffeinated and decaffeinated coffee appeared to decrease the risk for lethal prostate cancer. For each one cup per day increment, the risk declined by 6% for regular coffee (RR, 0.94; 95% CI, 0.88-1.01) and by 9% for decaffeinated coffee (RR, 0.91; 95% CI, 0.83-1.00; $P = 0.05$). Men drinking at least six cups a day had an age-adjusted incidence of only 425 prostate cancers per 100,000 person-years as opposed to 529 in those not consuming coffee. Likewise, the incidence of lethal prostate cancers was 34 vs 79 per 100,000 person-years in those drinking at least six cups vs nondrinkers, respectively. However, no association was found between coffee consumption and low-grade prostate cancers.

■ COMMENTARY

Coffee contains biological compounds that improve glucose metabolism, have anti-inflammatory and antioxidant effects, and affect sex hormone levels, all of which may have played a role in prostate cancer progression. In fact, coffee is a major dietary source of antioxidants for Americans. This study provides a strong association between coffee consumption and lower risk of lethal and advanced cancers and the authors state that this appears to be related to non-caffeine components of coffee. We currently have not identified modifiable risk factors for advanced prostate cancer, which is the second-leading cause of cancer death among American men after lung cancer. However, the analyzed data from this well-done large study (as well as some smaller ones in the past) are clearly insufficient for us to recommend that men start drinking gallons of coffee in an attempt to lower their prostate cancer risk.[4] We would need to see these results replicated in other large studies before we can be sure whether coffee consumption affects the risk of prostate cancer. Additionally, heavy caffeine use (four to seven cups of coffee a day) can cause other problems such as tachycardia, restlessness, anxiety, irritability and sleeplessness, gastroesophageal reflux, and risk of heart disease in susceptible people. Also, we must keep in mind that for those drinking more than plain coffee, supplements such as cream and sugar contribute fat and calories to the diet. Therefore, at this time I would stick to the old dictum, "Everything in moderation." ■

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Add Prunes to Your Toolkit for Constipation

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Dr. Scherger is Clinical Professor, University of California, San Diego, CA; he reports no financial relationships relevant to this field of study.

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Synopsis: *Dried plums (prunes) are safe and more effective than psyllium for treating mild-to-moderate constipation.*

Source: Attaluri A, et al. Randomised clinical trial: Dried plums (prunes) vs. psyllium for constipation. *Aliment Pharmacol Ther* 2011;33:822-828.

At the University of Iowa, 40 constipated subjects were randomized in an 8-week, single-blind crossover trial. Thirty-seven of the 40 were women and the average age was 38. The subjects took either prunes or psyllium for 3 weeks and then crossed over after a 1-week wash-out period. Fifty grams of prunes and 11 grams of psyllium were used equaling 6 grams of fiber each. The subjects maintained a daily symptom and stool diary. The study assessments included number of spontaneous bowel movements per week, global relief of constipation, stool consistency, straining, tolerability, and taste.

The subjects taking the prunes reported more complete spontaneous bowel movements per week (primary outcome measure) and stool consistency scores improved significantly compared to psyllium ($P < 0.05$). Straining and global constipation symptoms did not differ significantly between treatments. Dried plums and psyllium were rated as equally palatable and both were safe and well tolerated.

■ COMMENTARY

Constipation is one of the most common symptoms presenting to primary care physicians. Prevention and treatment often blur into one passionate request from patients for help. Patients vary in what they have tried and what appeals to them. Having a toolkit of several effective options helps us care for more of these suffering patients.

Adequate fluid intake and daily fiber are the mainstay of prevention. My favorite is a cereal concoction I eat every day combining some regular Cheerios (oat fiber), some Fiber One cereal, yogurt, a handful of sliced walnuts and some blueberries, moistened with low-fat milk. One of my partners has her own "poop pudding" focusing more on fruit than cereal. Not everyone tolerates gluten in large amounts and some get cramps from very much fruit.

My mother struggled with lifelong constipation and drank prune juice every night with limited success. When I put her on a high-fiber cereal in the morning as a medical student, my reputation in her eyes was set for life.

This is a small comparison study that puts prunes right up there with psyllium for constipation prevention and treatment, at least among younger women. When I mentioned this study to a perimenopausal patient, she quickly said that dried apricots work better for her than prunes. I know from first-hand experience that very much dried fruit of any kind will get your intestines going. Fruit juices are mostly sugar and are to be avoided. The fiber has been largely filtered out.

Too often I see physicians resorting to a bad habit learned in medical school, the "stool softener" docusate sodium (Colace). Docusate is far less effective than psyllium in managing constipation.[1]

Sometimes it is the small things to us that make a big difference with patients. I enjoy telling patients I can cure their constipation if they cooperate every day. They give me looks of joy or skepticism. Usually I am effective and I wonder how much of my reputation in the community is based on that. ■

Reference

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Desperate Diseases Call for Drastic Diets

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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This article originally appeared in the June 29, 2011 issue of Internal Medicine Alert. *At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *A very low energy diet followed by a weight maintenance program results in significant improvements in weight, obstructive sleep apnea, metabolic factors, and quality of life for at least a year.*

Source: Johansson K, et al. Longer term effects of very low energy diet on obstructive sleep apnea in cohort derived from randomised controlled trial: Prospective observational follow-up study. *BMJ* 2011;342:d3017.

This report is an extension of a shorter-term study conducted to assess the effects of a very low energy (or calorie) diet on obstructive sleep apnea. The study was conducted at the Obesity Unit at Karolinska University Hospital in Sweden. The participants were all obese men with moderate-to-severe obstructive sleep apnea who were stable on continuous positive airway pressure (CPAP). Patients were randomized to a very low energy diet or a control group for the first 9 weeks, but then the

control group was also started on the very low calorie diet after 9 weeks. After a 9-week very low energy diet period, both groups entered a weight loss maintenance program. Since the control group was only a control for the first 9 weeks, data from both groups were pooled for this 1-year follow-up analysis.

The very low energy weight loss diet was a 2.3 MJ/day (about 550 calories) liquid energy intake protocol (Cambridge Weight Plan, Northants, UK) for 7 weeks, followed by 2 weeks' gradual introduction of normal food to reach 6.3 MJ/day (about 1500 calories) at week 9. Patients were also scheduled for six visits with clinical examinations and group sessions. The maintenance program started right after the very low energy diet period and was essentially behavior modification group therapy supplemented with a self-help manual. Each group included 13-15 patients and was led by a research nurse and a dietitian. Each patient also was seen by a nurse for anthropometry measurements and a dietitian for individual dietary advice.

The protocol specified use of partial meal replacement as a first option (exchanging one or two daily meals with an approximately 140 calorie meal replacement) if the patient's weight had increased by more than 2 kg since the last visit. (Of note, almost all [86%] of the participants reported using partial meal replacement at least once). The secondary option was sibutramine or orlistat prescription, but orlistat was prescribed to only one patient.

Of the original 63 patients in the study, 49 completed sleep and adiposity follow-up measures (this included five people who dropped out of the weight maintenance program but were willing to follow-up), and 44 completed a full year of treatment.

At baseline, the majority of patients had severe obstructive sleep apnea, metabolic syndrome, hypertension, and dyslipidemia. Slightly more than half were obese; 56%, 41%, and 3% had BMIs of 30-34.9, 35-39.9, and ≥ 40, respectively. Their physical quality-of-life component was lower than in the general male Swedish population while the mental component was similar.

During the very low energy diet and full treatment program, weight, BMI, waist circumference, neck circumference, and percentage body fat all decreased significantly, but all these variables increased significantly during the weight maintenance period. Of the participants analyzed at the 1-year follow-up, one was normal weight (BMI < 25), 27 were overweight, and 35 (56%) remained obese (BMI ≥ 30).

All sleep variables improved significantly after the very low energy diet period and full treatment program, but then worsened significantly during the weight maintenance period. However, neither the weight nor the sleep-disordered breathing returned to baseline severity during 1 year of follow-up. Overall, the apnea-hypopnea index (AHI) fell by 58% after 9 weeks of a very low energy diet and was still statistically and clinically reduced (by 47%) at 1 year. At the 1-year follow-up, six patients (10%) had total remission of obstructive sleep apnea and 30 (48%) patients no longer required CPAP (23 of these did not need any further treatment and 7 shifted to treatment with an oral appliance). Improvements in the AHI were larger in those men with severe obstructive sleep apnea at baseline than in those with moderate disease. Patients who lost ≥ 15 kg had larger improvements in the AHI at 1 year than patients who lost less, but even modest weight loss resulted in significant improvement in AHI.

Between baseline and 1-year follow-up, the physical component of the quality-of-life score had increased by 4 units (2 to 6; $P < 0.001$) and was similar to that of the general population. Between baseline and 1-year follow-up all measured metabolic variables improved significantly. Dyslipidemia disappeared in 11/59, insulin resistance in 10/20, and metabolic syndrome in 23/44. Of those with hypertension at baseline, resolution occurred in 8/36 (22%).

During the very low energy diet period, 13 patients had an adverse event classified as probably causally linked with the very low energy diet, including constipation (n = 3), increased alanine aminotransferase activity (n = 6), dizziness (n = 1), gout (n = 2), and dry lips (n = 1). All adverse events had disappeared by the visit 2 weeks after the very low energy diet period. During weight loss maintenance there were five additional adverse events probably causally linked to treatment with very low energy diet, including gallstones (n = 3), gout (n = 1), and kidney stones (n = 1). No patient discontinued treatment because of adverse events.

■ COMMENTARY

Obstructive sleep apnea has roughly the same prevalence as asthma,[1] but is arguably more of a public health risk because it is associated not only with increased cardiovascular risk, but also with increased risk of moving vehicle crash.[2-4] CPAP treatment is effective, but CPAP adherence — while no worse than for any other medical treatment — is not optimum. The original report of this cohort[5] covered only 9 weeks of treatment, and the subjects were already regaining weight at the end of the first follow-up period after they left the very low energy diet and went to the maintenance program. I was among many skeptics who believed that neither the weight loss nor the improvement in sleep apnea would persist over time. This report has proved me wrong — though there were dropouts and failures, as a whole, the patients had significant, persistent improvements not only in weight and sleep apnea, but

also in metabolic factors and quality of life.

Indeed, while reading this report, I kept contrasting this approach to that of upper airway surgery such as uvulopalatopharyngoplasty (UPPP). UPPP has about the same short-term "cure" rate as is reported here (50%), but we don't know very much about its effects on blood pressure, metabolic factors, and quality of life. Indeed, long-term follow-up of those who undergo UPPP is uncommon, but we do know that relapse occurs, mostly related to weight gain.[6] The weight loss protocol in this study was extensive and labor-intensive, but almost certainly cheaper than surgery. And the adverse events (dry lips, gallstones) for the very low calorie approach pale in comparison to those related to UPPP (speech change, palatal stenosis, and, er, death).

Talking to patients about weight loss is hard. Getting them into programs is even harder. But this report suggests that it can really make a difference. One of my favorite lines in clinic is, "You are a smart person, and you have struggled with this for a long time. If you were going to lose weight on your own, you would have done it by now. Let's get some help." ■

CME Instructions

To earn credit for this activity, please 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 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.

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CME Questions

29. Melatonin production peaks at:
a. 9 p.m. and 11 p.m.
b. 2 a.m. and 4 a.m.
c. 6 a.m. and 8 a.m.

30. Large-scale human studies have confirmed the benefits and risks of the over-the-counter supplement melatonin.
a. True
b. False

31. In the coffee consumption and prostate cancer risk study by Wilson et al, which of the following appeared to decrease risk for lethal prostate cancer?
a. Caffeinated coffee
b. Decaffeinated coffee
c. Both
d. Neither

32. From the Attaluri study, which is the most effective and best tolerated for managing mild-to-moderate constipation?
a. Psyllium
b. Dried plums (prunes)
c. Docusate sodium
d. Fiber One cereal

33. For obese patients with obstructive sleep apnea, a very low energy diet followed by a weight maintenance program for 1 year:
a. is less effective at treating sleep apnea than is uvulopalatopharyngoplasty.
b. results in persistent significant weight loss and improvement in sleep apnea.
c. does not improve metabolic factors such as dylipidemia or diabetes.
d. is associated with serious adverse events, necessitating discontinuation of treatment.

In Future Issues:

Reiki: A Review

Observation to Measurement: How Research Gets Started