

Integrative Medicine

The Clinician's Evidence-Based Resource on Complementary Therapies [ALERT]

WOMEN'S HEALTH

Mind-Body Medicine and Menopause

By Judith Balk, MD

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

Menopausal women anecdotally report that their hot flashes are worse with stress;¹ for instance, if a woman has an unpleasant confrontation, she notices that it will trigger a hot flash. Research supports these anecdotal experiences. Lab stressors such as arithmetic tasks can also increase hot flashes. When women are randomized to a lab stressor condition vs a non-stress condition, those in the stress condition have 47-57% more hot flashes.² Women are not just reporting more hot flashes during periods of stress; objective measurements of hot flashes confirm the increase during stress conditions. Stress appears to lower the threshold for hot flashes to occur.

The exact causes of hot flashes are unknown; they are likely related to changes in thermoregulation due to fluctuations in estrogen concentrations.

Noradrenergic mechanisms also are implicated in thermoregulation, with epinephrine concentrations increasing during menopausal hot flashes.³

Not only does it appear that stress can worsen hot

flashes, but many women with hot flashes report negative emotions due to their hot flashes, including psychological distress and social embarrassment.⁴ Also, women with hot flashes have lower scores on the Stress Coping Inventory than women without hot flashes, and estrogen treatment that resolves hot flashes does not improve the Stress Coping Inventory Scores.⁵ This actually may indicate lower stress-coping skills in women who seek medical care for hot flashes. Since the stress response can trigger hot flashes, an obvious follow-up question is whether stress reduction or elicitation of the relaxation response could reduce hot flashes, both as treatment and for prevention. Mind-body medicine is one approach for eliciting the relaxation response. This article will review the evidence for mind-body therapies for treatment of menopausal hot flashes.

Small studies conducted many years ago provided preliminary evidence that relaxation techniques might improve the frequency and/or severity of hot flashes. Using heat-induced hot flashes as the outcome variable, one pilot study randomized 14

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women to sessions of either progressive muscle relaxation and slow deep breathing, or a control procedure (EEG biofeedback⁶). At the end of treatment and at 6-month follow-up, hot flash frequency was statistically significantly reduced in the experimental group but not in the control group. A second study aimed to determine whether the progressive muscle relaxation or the slow deep breathing was responsible for the therapeutic effect of decreased hot flashes found in the first study.⁷ Thirty-three women were randomized to one of three behavioral interventions: paced respiration, progressive muscle relaxation, or the control condition, EEG biofeedback. Subjects undergoing paced respiration had significant reductions in hot flash frequency, but the other groups did not. The paced respiration group learned slow, deep abdominal breaths at six to eight cycles/minute. Another small study randomized 33 women to one of three groups: relaxation response training, attention control (leisure reading), or control (symptom diary).⁸ The relaxation response group had significant reductions in hot flash intensity, and the other two groups did not.

Since the time of these small studies, larger studies have focused on the use of mind-body medicine to manage hot flashes. Mindfulness based stress reduction (MBSR) is a standardized program developed by Jon Kabat-Zinn. Instruction is widely available and involves eight weekly 2.5 hour classes, plus an all-day class on a weekend day during the sixth week. The standardized curriculum includes a body scan, sitting meditation, and mindful stretching exercises. Participants receive CDs and practice the guided instruction at home. This same standardized program was used in a randomized, controlled study of 110 women randomized to either MBSR or a waitlist control.⁴ Both bothersomeness and intensity of hot flashes were measured, as well as psychosocial variables including quality of life, anxiety, perceived stress, and subjective sleep quality. At the end of the intervention period, hot flash bothersomeness had statistically improved from baseline in the MBSR

group (95% confidence interval [CI], 7.94%-21.61%, $P < 0.00001$) but not in the control group (CI, -0.24%-13.81%; $P = 0.062$); however, differences between groups were not statistically significant. Overall trajectories for within-woman change differed significantly by treatment arm ($P = 0.042$). Hot flash intensity improved in both groups over the course of the study, with no difference between groups. Quality of life ($P = 0.022$), subjective sleep quality ($P = 0.009$), anxiety ($P = 0.005$), and perceived stress ($P = 0.001$) each improved in the MBSR participants compared to the control participants, and these improvements were maintained at 3 months post-intervention. Overall, MBSR appears to be an intervention that is likely helpful during the training, with continued improvements post-training.

Because hot flashes may trigger uncomfortable emotional reactions, one approach to managing the hot flash is to focus on managing the emotional reaction. For instance, if catastrophic thoughts moderate the experience of hot flashes, then cognitive behavioral therapy (CBT) may be helpful in symptom management because it may reduce catastrophic thinking. CBT was studied in menopausal women experiencing problematic hot flashes.⁹ Participants were randomized to either group CBT, a guided self-help CBT, or to a no-treatment control group. The group CBT and the self-help CBT had identical content, and both included the same daily home practice with CDs and weekly homework tasks. The primary outcome was hot flash problem rating (a standardized rating scale with good internal consistency and test-retest reliability) at the end of the 6-week intervention, and secondary outcomes included hot flash problem rating at 6 months, hot flash frequency, mood, and quality of life. Both group and self-help CBT significantly reduced hot flash rating and night sweat frequency at 6 weeks and at 6 months compared to the no-treatment control group. Also, mood and multiple quality of life domains improved (CI 0.01-0.15, $P = 0.045$ and $P < 0.04$ QOL domains) at 6 weeks and emotional and physical functioning improved at 6 months in the CBT group (CI, 1.06-

Summary Points

- Stress appears to increase the occurrence of menopausal hot flushes.
- Stress reduction techniques can decrease hot flushes and improve quality of life, anxiety, and sleep.
- Evidence exists for mind-body modalities including mindfulness training, hypnosis, and cognitive-behavioral therapy to reduce hot flashes.

27.90, $P = 0.035$ and CI 0.89-12.22, $P = 0.023$, respectively). Both group and self-help CBT seem to improve menopausal hot flashes.

Breast cancer patients often seek alternatives to hormone therapy for management of hot flashes, because menopausal hormone therapy is contraindicated. Multiple studies have evaluated mind-body medicine, including hypnosis, CBT, and relaxation training, for management of hot flashes in breast cancer patients. In one trial, 60 breast cancer survivors with hot flashes were randomized to either weekly hypnosis or to no treatment.¹⁰ The hypnotic suggestions for each session included mental imagery for coolness, dissociation from hot flashes, and others. The primary outcomes were hot flash frequency and a hot flash score, with secondary outcomes being degree of hot flash interference with daily activities, mood, and sleep. Hot flashes, sleep, and mood each statistically improved in the treatment group relative to the control group, with a large effect size. Hot flash scores decreased 68% in the hypnosis intervention group; the authors do not report the decrease in the control group, but it appears to be < 15% based on review of their graph. Longer-term studies using an attention control group are warranted, but the preliminary evidence is promising. The same investigators conducted a randomized controlled trial of hypnosis in a general population; the abstract was presented at a recent research meeting.¹¹ In this trial, 187 participants were randomized to either hypnosis ($n = 93$) or to a structured attention ($n = 94$) in which the control group received the same amount of contact and attention. Hot flashes significantly decreased in the hypnosis group relative to the control group. The manuscript with a full description has been submitted per the author.

CBT, as described above, also has been studied for menopausal symptoms in breast cancer survivors.¹² Ninety-six participants were randomized to group

CBT plus usual care or to usual care alone. Usual care included typical follow-up appointments every 6 months with additional appointments as necessary, optional telephone support as part of the cancer survivorship program, and written information. Participants met weekly for 6 weeks and learned psycho-education, paced breathing, and cognitive and behavioral strategies to manage their hot flashes. Group CBT significantly reduced hot flash rating compared with usual care, and improvements were maintained at 6 months. Additionally, mood, sleep, and quality of life all improved in the CBT group. Careful assessment of safety indicated no adverse events related to CBT.

Another trial focused on 150 breast cancer survivors who were randomized to either relaxation training or no intervention.¹³ The intervention group received a single relaxation training session and 1 month of daily home practice using tapes. Outcomes were frequency and severity of hot flashes, anxiety, and quality of life. Hot flash frequency and severity both statistically declined compared to the control group over the 1-month study period. At 3 months, no differences existed between groups, and anxiety and quality of life were unaffected. Longer intervention period and an attention control group would improve the science, but the intervention as studied is a low-cost, minimal subject burden intervention that might be helpful for breast cancer patients.

SUMMARY

Mind-body approaches such as MBSR, cognitive behavior therapy, hypnosis, and relaxation training may improve the frequency, severity, and bothersomeness of menopausal hot flashes. Many studies do not report adverse events, but they appear to be rare and include skin irritation from the monitors used to measure hot flashes and possible mood deterioration from participating in mind-body modalities. The current literature is limited by few long-term studies using either attention control groups or known active treatment. That said, suggesting stress reduction techniques and coping skills training will likely enhance a patient's quality of life and experience during menopause. ■

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CHRONIC DISEASES

High-Intensity Interval Training: A Sprint or Nine Saves Time?

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Strong evidence supports regular exercise as a lifestyle habit and intervention that lowers risk for a myriad of diseases including coronary heart disease, high blood pressure, type 2 diabetes, obesity, and breast and colon cancers.¹ In addition, exercise has gained treatment status for cardiometabolic risk factors, type 2 diabetes, osteopenia and osteoporosis, and rehabilitation for existing cardiac disease. Current guidelines for healthy adults recommend a minimum of 150 minutes per week of moderate aerobic exercise or 75 minutes per week of intense aerobic exercise.¹ However, only 64.5% of U.S. adults are able to meet these federal recommendations.² Guidelines also state that additional time accrued during exercise is associated proportionally with increasing health benefits. For maximum benefits, muscle strengthening, stretching, and balance exercises are recommended in addition to this baseline time commitment to aerobic exercise.^{1,3} It is no surprise that “lack of time” is one of the main barriers to regular exercise cited by adults.⁴

High-intensity interval training (HIT) is characterized by “burst” type exercise efforts at 90% or more of $\text{VO}_{2\text{max}}$ or maximum aerobic capacity for short periods of time interspersed with periods of low-intensity exercise or rest. This kind of exercise has been studied and used for decades to improve performance in competitive athletes, but recently there has been a growing research interest into the possible physiologic benefits of HIT, both for healthy and clinical populations. Because of the

short lengths of intense exercise interposed with recovery periods, untrained individuals are able to work harder than they would otherwise during more prolonged continuous exercise. It has been shown that the physiologic adaptations to HIT appear to be superior to continuous moderate exercise (CME). HIT protocols offer additional potential advantages in that the total exercise volume and time commitments are 10-90% less than matched-work CME protocols. Thus, if HIT offers metabolic and health benefits equal to or greater than continuous moderate activity and in less time, it could be an acceptable solution to the “time excuse” that prevents patients from exercising.

PHYSIOLOGIC EFFECTS OF HIT

To assess the potential benefits of HIT, the physiological effects of such interventions need to be elucidated. In a series of such studies, Gibala et al showed a variety of physiological and biochemical adaptations using a Wingate HIT protocol, consisting of 4-6 sets of intervals of 30 seconds of all-out cycling effort against a supra-maximal workload followed by 4 minutes of recovery. These authors showed that as little as 2 weeks of this protocol, totaling 18-27 minutes of total exercise per session performed three times weekly, resulted in increased maximal activity and concentration of mitochondrial enzymes, consistent with increased skeletal muscle oxidative capacity. After several weeks of this HIT protocol, compared to a CME program designed to be consistent with current public health recommendations for aerobic

Summary Points

- High-intensity interval training (HIT) alternates brief periods of near maximal intensity with slightly longer periods of low-intensity activity or rest.
- HIT may be an ideal form of exercise for people with significant time constraints.

exercise, the authors found similar improvements in skeletal and cardiovascular markers for adaption, including increased resting muscle glycogen content, increased capacity for lipid oxidation, decreased glycogen utilization and lactate production, enhanced peripheral vascular function, and increased exercise performance and $\text{VO}_{2\text{max}}$. Subsequently, the same authors, in a series of small “proof of principle” studies using a modified protocol that was more practical and tolerable, consisting of 10 sets of 10-second, high-intensity cycling using a constant workload at about 90% maximal heart rate alternating with 60 seconds of recovery, demonstrated the same effectiveness at producing skeletal muscle metabolic adaptations as shown in their previous HIT protocol and higher volume endurance training.⁵ This latter protocol clearly offers a time advantage requiring only about 12 minutes per exercise session. The authors claim that the metabolic changes occurring in muscle with both CME and HIT are mediated by similar mechanisms; both induce activation and nuclear concentration of PGC-1 α , a master regulator protein of muscle mitochondrial biogenesis.⁶ A modest increase in muscle PGC-1 α appears to have a beneficial effect on oxidative capacity, antioxidant defense, anti-inflammatory pathways, glucose utilization, and prevention of age-related muscle loss. Thus, a significantly lower volume of exercise than is currently recommended, performed at higher intensity, appears to have significant potential health benefits.

CLINICAL RESEARCH

Although physiological and clinical evidence is vital, this needs to be translated to clinical relevance. In support of this approach, Kessler et al reviewed research evidence for HIT in reducing the risk of cardiometabolic disease and separated HIT protocols into two distinct types performed on a cycle ergometer or a treadmill.⁷ Using young healthy subjects (because of potential health, safety, and motivational concerns), sprint interval training (SIT) was used to represent the Wingate HIT protocol described above. Aerobic interval training (AIT),

on the other hand, had protocols using 4-6 sets of 4 minutes of high-intensity work at 80-95% $\text{VO}_{2\text{max}}$ followed by 3-4 minutes of recovery. AIT studies in this review included young healthy subjects as well as older and clinical populations as compared to the SIT studies.

Of the studies reported by Kessler, 17 examined the impact of HIT on exercise capacity, with all showing improvement in $\text{VO}_{2\text{max}}$.⁷ Four of the HIT studies were of 4-8 weeks duration and compared HIT to CME; the improvements in $\text{VO}_{2\text{max}}$ were similar in the HIT and CME arms. In contrast, differences were noted in the studies of longer duration. In nine AIT studies of 10 weeks to 6 months duration, all but one resulted in greater improvement in $\text{VO}_{2\text{max}}$ compared to CME. When reported, P values ranged from < 0.05 to < 0.001, demonstrating statistical significance. The one study failing to demonstrate any improvement in $\text{VO}_{2\text{max}}$ over an 11-week training period used an alternate AIT protocol of eight sets of 2-minute duration, high-intensity intervals. This somewhat surprising finding could be due to small sample size and the fact that the ideal HIT protocol proportion of exercise and rest is as yet unknown. In contrast, an SIT study of only 2 weeks’ duration and an AIT study of only 4 weeks’ duration showed significant improvements in $\text{VO}_{2\text{max}}$ induced after only a few training sessions. In Kessler’s review, 13 studies examined HIT impact on biochemical parameters such as glucose metabolism, insulin sensitivity, and fasting glucose as well as oral glucose tolerance. Of these 13 studies, seven measuring insulin sensitivity after HIT showed significant improvement.⁷ Three of these studies included subjects who were obese, had a family history of hypertension, or had metabolic syndrome. In those studies described in the review that included a CME arm, improvements with HIT were similar in both exercise groups. Eleven studies also assessed fasting glucose levels. Three 2-4 week duration SIT studies showed no changes from baseline values in fasting plasma glucose; the studies of longer duration revealed results that were inconclusive. For example, seven AIT studies of 12-16 weeks’ duration reported inconsistent results in fasting plasma glucose after AIT, with four trials reporting reductions and three reporting no change in subjects with normal, borderline, and elevated baseline values. However, all five HIT studies that reported results for oral glucose tolerance testing showed significant improvement in the 2-hour postprandial glucose or glucose area under the curve (AUC) measurements. Measuring oral glucose tolerance could be a more reliable marker than measuring fasting plasma glucose alone and needs further investigation.

From a biochemical perspective, the association

of blood lipids and cardiovascular disease under these exercise conditions also would need to be considered. In this respect, HIT was shown to have less of an impact on lipid measurements, unfortunately. Of the lipids measured, only high-density lipoprotein cholesterol (HDL-C) was beneficially affected by HIT, and only three of 10 studies lasting at least 8 weeks showed any improvement. HIT was comparable to CME in this regard, though.⁷

A reduction in elevated blood pressure with exercise training is indeed a desirable outcome. In this respect, of 12 studies that examined the effect of HIT on blood pressure, most that were of 2-10 weeks' duration showed no change. A single, 2-week SIT study showed a transient decrease in systolic blood pressure 24 hours after exercise that did not persist at 72 hours. Five studies of AIT of longer duration (12-16 weeks), in subjects who were not on blood pressure medication, showed a variable decrease in blood pressure. In AIT studies of subjects on antihypertensive medications, no significant change in blood pressure was noted, though all study subjects had well-controlled blood pressure at baseline.⁷

From a broader perspective, biochemical and clinical parameters should be viewed together with morphological characteristics, as these are also predictors of health outcomes. Seventeen studies measured the impact of HIT on anthropomorphic measurements such as body weight, BMI, body-fat percentage, lean body mass percentage, waist-to-hip ratio, and waist circumference. Improved measurements were observed only in studies of > 10 weeks' duration, except for one 2-week study using SIT that reported an average 2.4 cm reduction in waist circumference in obese young men. In studies comparing HIT to CME, such outcomes were comparable.⁷

In a meta-analysis of six AIT randomized, controlled trials including 153 patients with cardiometabolic disorders, Huang et al reported similar conclusions. These authors also reported a high adherence rate of > 70% in three trials and > 90% in two trials. A total of only 10 patients withdrew, five from the AIT group, four from the CME group, and one from an undetermined group, and all for reasons not directly related to the exercise intervention. No exercise-related adverse events were reported in this meta-analysis,⁸ nor in the larger review by Kessler.⁷

For long-term exercise compliance, subjects need to be motivated by enjoying the activity. Surprisingly, only a few studies have addressed subjects' perception of HIT. Though HIT is often

given a higher rate of perceived exertion by patients, Bartlett et al reported higher ratings of perceived "enjoyment" for HIT compared to CME.⁹ This finding was corroborated in a study by Wisloff et al, who showed that heart failure patients experienced HIT as more motivating than CME, which in turn was perceived as "boring."¹⁰

CONCLUSION

The findings to date on HIT for health maintenance and for prevention and treatment of cardiometabolic diseases are intriguing. HIT appears to be as effective as CME, if not more so, for increasing maximum exercise capacity, improving insulin resistance and blood pressure, reducing body fat, and raising HDL-C. Many questions and concerns still need to be addressed. The ideal dose of HIT in terms of exercise and recovery ratios and total volume of HIT exercise has not been clearly established, and may differ greatly depending on patient goals and therapeutic targets. The absolute minimum amount of exercise needed to reduce cardiometabolic risk still needs to be established. Epidemiologic evidence from a Norwegian study suggests that a single weekly bout of high-intensity exercise is associated with a significantly lower risk of cardiovascular disease.¹¹ Further, Metcalfe et al recently found that cycling 10 minutes at low intensity with just one or two burst efforts of sprints lasting 10-20 seconds, three times per week, resulted in improved insulin sensitivity and increased $\text{VO}_{2 \text{ max}}$.¹² The studies to date have had heterogeneous patient populations. Even though results look promising for HIT as a therapeutic intervention, studies of larger samples of more homogeneous populations with cardiometabolic risk factors or disease will help support these initial data. Studies of longer duration will help determine if additional benefits accrue and if HIT is sustainable for various populations. HIT is a highly structured and individualized exercise program and requires at least some initial education and supervision. For example, to reach 90% of maximal exercise capacity, some healthy individuals will need to perform all-out cycling against a significant load, while a patient with heart failure may achieve the same exercise intensity with slow treadmill walking up a slight incline. Though using rate of perceived exertion can help with self-monitoring of exercise intensity, it seems prudent to initiate an HIT program with close supervision and heart rate monitoring, at least in clinical populations. Most studies reported that subjects were verbally encouraged during the high-intensity intervals, which might artificially increase motivation, ability, and adherence compared to a home program. Many of the HIT trials to date have been performed in the same laboratory, introducing possible investigator bias.

RECOMMENDATION

HIT may be an ideal form of exercise for people with time constraints who wish to be fit and reduce disease risk. Certainly, it may be a way to help inactive patients segue into a more active lifestyle since it so rapidly increases exercise tolerance. The fact that heart failure patients in one study found HIT more motivating than constant moderate exercise suggests that sedentary inactive people with low baseline exercise capacity may find HIT a quite acceptable way to start a fitness program. However, it is clear that education and supervision are indicated for this kind of exercise to ensure safety and effectiveness, especially for sedentary people, those with risk factors for cardiac disease, or for those with established disease. Large multicenter trials of longer duration, including home programs, are essential before HIT can be included in our exercise prescriptions for patients with confidence. ■

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OBESITY

ABSTRACT & COMMENTARY

Don't Just Sit There: Sitting, TV Viewing, and Mortality

By Russell H. Greenfield, MD

SYNOPSIS: Findings from this unique investigation add a new wrinkle to concerns over the increasingly sedentary nature of American society. They also suggest that years could be added to general life expectancy simply by limiting time spent sitting and TV viewing.

SOURCE: Katzmarzyk PT, et al. Sedentary behaviour and life expectancy in the USA: A cause-deleted life table analysis. *BMJ Open* 2012;2: pii: e000828. doi: 10.1136/bmjopen-2012-000828.

 One would have to live under a rock (thereby getting very little exercise...) to be unaware of the importance of regular physical activity to overall health. The converse, that a couch potato lifestyle does not promote optimal health, is also widely recognized. Putting two and two together, it makes sense that regular exercise should counteract the adverse effects of a sedentary lifestyle — but what if they are independent, and not codependent, health risk variables?

The authors of this sobering investigation sought to determine the impact of sedentary behaviors, specifically sitting and television viewing, on life expectancy in the United States using a prevalence-

based, cause-deleted life table analysis (a tool that estimates probability of death over time). Studies addressing the relationship between sitting or television viewing and all-cause mortality were identified through a systematic literature search of MEDLINE and were included if they provided relative risk (RR) estimates along with 95% confidence intervals (CIs). Trials that reported on the relationship between sedentary behaviors and outcomes other than all-cause mortality and those not using a prospective observational cohort design were excluded. Abstracts and papers were reviewed by both authors and discrepancies resolved by consensus. RR estimates from each study for sitting or television viewing and all-cause mortality were

Summary Points

- Sitting or television viewing appear to reduce population-based life expectancy in the United States.
- Exercise may not completely offset the untoward effects of many hours spent sitting or watching television.

pooled using a random effects meta-analysis. Pooled RR estimates were obtained for two levels of sitting and two levels of television viewing, and age- and sex-adjusted RR estimates were used from each study. The prevalence of time spent sitting (2009-10) and television viewing (2005-6) were obtained from the National Health and Nutrition Examination Survey (NHANES). The population-attributable fraction (PAF) was computed from the prevalences of sitting and television viewing and the RR of all-cause mortality associated with those behaviors using an equation that reportedly produces internally valid estimates when confounding exists and adjusted RRs must be used. The specific PAF equation used requires the prevalence of sedentary behaviors among cases (those who have died, in this instance) rather than from the source population (in this case, NHANES prevalence). Potential gains in life expectancy associated with a reduction in sitting and television viewing were estimated using a cause-deleted life table analysis, focusing on adults aged 40-79 years. This approach estimates the number of years of life gained at birth if deaths from a specific cause are eliminated from the current death rates. The difference between current life expectancy and cause-deleted life expectancy thus represented any estimated gain in lifespan from reducing the prevalence of sitting and watching television.

The literature search yielded a total of 460 abstracts for review, of which almost all (455) were excluded, the primary reason being that the studies did not address either sitting or television viewing as an exposure and all-cause mortality as the outcome ($n = 400$). Two studies examined the association between sitting and all-cause mortality; the other three focused on the relationship between TV viewing and all-cause mortality. Together the investigations provided data from almost 170,000 subjects, almost 75% coming out of one trial.¹

Pooled RRs for sitting and all-cause mortality were 1.18 (95% confidence interval [CI] 1.14 to 1.21) and 1.45 (95% CI 1.39 to 1.51) for the mid- and highest levels of sitting compared to the lowest, respectively. For the meta-analysis of television viewing and all-

cause mortality, the pooled RRs were 1.17 (95% CI 1.04 to 1.32) and 1.49 (95% CI 1.22 to 1.82) for moderate and high levels of TV viewing compared with the lowest, respectively. PAFs for all-cause mortality associated with sitting and television viewing were 27% and 19%, respectively. Life table analyses showed that reducing the prevalence of sitting to < 3 hours per day could result in a gain of 2.00 years of life, while limiting TV viewing to < 2 hours a day could produce a gain of 1.38 years in life expectancy. The lower and upper limits from the sensitivity analyses were 1.39 and 2.69 years for sitting and 0.48 and 2.51 years for television viewing, respectively. The authors conclude that extended time sitting and television viewing likely reduces life expectancy in the United States.

COMMENTARY

Increasing the level of physical fitness in our communities is, and has long been, a major public health initiative. And many have heeded the call, some by joining gyms, others by increasing their activity throughout the day. There seems to be a general movement toward increased movement. This is good news, because it is clear that regular physical activity contributes to improved physical and emotional health. Yet questions persist — for example, could high levels of sedentary behavior be an independent risk factor for morbidity and mortality? Think about it — most of you reading this article exercise on a regular basis (I hope), yet we also spend many hours in the seated position. Guidelines regarding physical activity to promote good health are explicit — should we also be sharing similarly explicit guidelines about sedentary activity with our patients, and following those guidelines ourselves? The results of the current study pointedly suggest that a renewed emphasis on limiting sedentary behaviors is in order.

The authors do a nice job reviewing the literature on the relationship between sedentary behavior and illness around the globe. Not surprisingly, the results support their findings — sitting and television viewing have a major negative impact on public health.

A prospective trial addressing this issue would be impractical at best, so the authors took a different approach. Their conclusions could be dinged for being based on results from only five trials; however, data were culled from a large number of participants. The researchers readily point out that their study relied on self-reported participation in sedentary behaviors, introducing concern over recall bias, and that some assumptions were made regarding NHANES data. They also explain that the equation used for PAF only provides a theoretical

estimate of the effects of a given risk factor on a given outcome at the population level, the outcome in this instance being all-cause mortality, and that from the start they assumed a cause-effect relationship between sedentary behavior and mortality risk.

It's important to keep in mind that even though the conclusions reached in this paper are alarming, it would not be appropriate to attempt to apply them to individual risk; life expectancy is a population statistic that does not readily translate to individuals, and potential confounders are numerous.

We are left to ponder a troubling notion — that the effects of sedentary behavior on health may be independent of the effects of physical activity. A cottage industry has recently sprung up around

treadmill desks to lessen time spent sitting at work — aside from concerns over the potential for traumatic injury (coordination being a challenge for this reviewer), it could be a good idea. At the very least, it seems we should be asking people to get up and move about at regular intervals. The idea is not new but the data are increasingly convincing. Piling on the miles walking or running while wearing the latest in footwear, among other activities, is clearly good for our health but may not be enough to fully counter the effects of the largely sedentary style of living our society promotes. It appears we need not only figure out how to get people to move to promote optimal health, but also how to simply get them out of their chairs. ■

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AGING

ABSTRACT & COMMENTARY

The Vitamin D and Mobility Connection

By David Kiefer, MD

Research Fellow, Department of Family Medicine, University of Wisconsin; Clinical Assistant Professor of Medicine, Arizona Center for Integrative Medicine, University of Arizona

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

SYNOPSIS: Low serum 25-hydroxyvitamin D correlates with the development of mobility limitations and disability in older people who were otherwise healthy.

SOURCE: Houston DK, et al. Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: The Health ABC Study. *J Gerontol A Biol Sci Med Sci* 2012; 67A(1):1-7.

Stretching the boundaries of vitamin D thinking and dovetailing with prior work connecting vitamin D intake or supplementation and serum 25-hydroxyvitamin D (25(OH)D) levels with muscular function and many other medical conditions, the researchers behind this study sought to further examine the relationship between vitamin D and mobility in adults.

The study started with 3075 initially well, community-dwelling men and women, black and white, ages 70-79, from Pittsburgh and Memphis. After excluding those with missing serum 25(OH)D levels or who had limited mobility during the second year of the trial, a total of 2099 people remained to be followed for the 6 years of this analysis. Serum 25(OH)D and parathyroid hormone (PTH) were measured at the year 2 visit. The occurrences of mobility disability and limitations were assessed by an annual clinic visit and phone calls every 6 months. Information about a variety of confounding variables also was collected, such as the season during which blood was collected (addressing

the expected higher 25(OH)D levels during the summer), demographics, exercise, smoking status, and dietary supplement and alcohol intake.

The breakdown for serum 25(OH)D levels for the 2099 people in the study was as follows: 35% ≥ 75 nmol/L, 36.1% 50 to < 75 nmol/L, and 28.9% < 50 nmol/L. With respect to the mobility part of the equation, 36.3% reported a mobility limitation during the 6 years, while 22.0% reported a mobility disability. The researchers used two statistical models depending on which possible confounding variables were included, which then compared the people in the different 25(OH)D groups with their mobility limitations and disabilities. With these models, the researchers found a greater risk of mobility limitation and disability when the groups with a 25(OH)D < 50 nmol/L and 50 to < 75 nmol/L were compared to those with levels ≥ 75 nmol/L ($P = 0.02$ to < 0.001). Even the models including the most confounding variables showed this trend. With respect to PTH, those participants with an elevated PTH (≥ 70 pg/mL) had a higher risk of mobility limitation and disability than those with a low PTH

(< 27 pg/mL). The researchers calculated that people with serum 25(OH)D < 50 nmol/L were at twice the risk of mobility problems, whereas those with serum 25(OH)D < 75 nmol/L were at a 30% higher risk.

COMMENTARY

Hints in the medical literature should have made our response to these results “Of course” or “It seems reasonable.” Although some inconsistencies exist, several prior studies, detailed nicely by the authors in their introduction, have found impaired strength and physical performance and self-reported limitations in mobility in older adults. In addition, the mechanism apart from changes associated with normal aging exists: Vitamin D is important not only for bone health (clearly relevant to mobility), but also to overall calcium, phosphorus, and magnesium metabolism, minerals that are involved with muscle function.¹ The results seem convincing enough to add mobility to our list of why adequate vitamin D levels are important for maintenance of good health. Ideally, the researchers would have had more than one laboratory value (rather than just at year 2), and not relied so heavily on self-reported mobility limitations and disability. That said, the size of the trial, the inclusion of numerous possible confounding variables, and statistically significant findings were all positive aspects of this study. Presumably, the next step would be a prospective intervention trial comparing vitamin D supplementation (or dietary intake or sunlight exposure), and the resulting serum 25(OH)D levels, with placebo, for people with low serum levels to determine if such remediation would be of benefit in the realm of mobility.

Summary Points

- Studies strongly suggest that adequate levels of vitamin D may help promote not only bone health but also proper muscle function.
- Results of this study show that adequate vitamin D levels help reduce the risk for mobility limitation and disability.

Putting the results into the units of measure for 25(OH)D levels most commonly used, the cutoffs in this study would be < 20 ng/mL, 20 to < 30 ng/mL, and ≥ 30 ng/mL, arguably still within the lower range of ideal vitamin D levels.² How might this affect our interpretation of these results? If anything, it would strengthen the demonstrated association; imagine comparing the lowest tertile to a group in the range 40-50 ng/mL that some experts recommend and for which some evidence exists for improved mobility. The authors touch on this issue, lightly criticizing the Institute of Medicine recommendation that, for ideal bone health, people have a serum 25(OH)D > 20 ng/mL. ■

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CANCER

ABSTRACT & COMMENTARY

Dietary Lignan Intake and Breast Cancer Risk

By Donald J. Brown, ND

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Dr. Brown is a consultant to the supplement industry. He reports no financial relationships relevant to this field of study.

Synopsis: In this case-control study, dietary lignan intake was inversely associated with risk of breast cancer in both premenopausal and postmenopausal women. Also noted were more favorable prognostic characteristics associated with lignan intake, especially in premenopausal women.

Source: McCann SE, et al. Dietary intakes of total and specific lignans are associated with clinical breast tumor characteristics. *J Nutr* 2012;142:91-98.

To evaluate the relationship between dietary lignan intake and breast cancer as well as tumor characteristics, the researchers investigated dietary intakes of total and specific lignans in 683 women with breast cancer and 611 healthy women enrolled in the Data Bank and BioRepository (DBBR) at Roswell Park

Cancer Institute (RPCI) in Buffalo, NY. The total population of premenopausal women was 214 with breast cancer (mean age 44.6 years) and 202 controls (mean age 44.4 years). In the group of postmenopausal women, there were 469 with breast cancer (mean age 63.7 years) and 409 controls (mean age 62.1 years). Clinicopathologic data were

obtained from the RPCI breast cancer database. The data were linked with epidemiologic data from the DBBR and included tumor stage and grade, estrogen receptor (ER) and progesterone receptor (PR) status, and HER2 protein expression. Daily intakes of total lignans and found individual lignans (matairesinol, lariciresinol, pinoresinol, and secoisolaricresinol) were obtained from a food frequency questionnaire that was part of the DBBR. Odds ratio [OR] and 95% confidence interval [CI] for associations between daily intakes of total and specific lignans with clinicopathologic characteristics compared to women without breast cancer were estimated.

Women in the highest compared to the lowest tertile of total lignan intakes had approximately 40-50% lower odds of having breast cancer. Higher total lignan intakes also were associated with significantly reduced odds of having an invasive tumor, especially among premenopausal women (OR 0.48 [95% CI 0.26-0.86] for premenopausal women and OR 0.70 [95% CI 0.47-1.06] for postmenopausal women).

The reductions in risk of breast cancer and invasive cancer were linked primarily to higher intakes of lariciresinol and pinoresinol in premenopausal women and of lariciresinol and matairesinol in postmenopausal women. For premenopausal women, there was a borderline significant 50% reduction in odds of having either stage I or II breast cancer but no association with higher stages. The association was strongest for the lignans lariciresinol and pinoresinol. In postmenopausal women, there was a significant 50% reduction only in stage I cancers that was associated with increased intake of matairesinol. Higher total lignan and matairesinol intakes were associated with lower risk of grade 3 tumors, primarily among premenopausal women.

Higher total lignan intakes were strongly inversely correlated with risk of ER⁻ breast cancer among premenopausal women (OR 0.16 [95% CI 0.03-0.44]) independent of the specific lignan. Among postmenopausal women there was an inverse correlation related to ER⁺ breast cancer that was predominantly associated with lariciresinol and matairesinol intakes. Higher intakes of total lignans were associated with both negative and positive HER2 status in premenopausal women, with the estimates much stronger for HER2⁺ (OR 0.21 [95% CI 0.05-0.87]) than HER2⁻ (OR 0.56 [95% CI 0.30-1.05]). There was no association between total lignan intakes and HER2 status in postmenopausal women, but there was a lower risk of HER2⁺ tumors in those consuming higher amounts of matairesinol (OR 0.36 [95% CI 0.14-0.89]). Among premenopausal women, those in the highest tertile of total lignan intake had greatly reduced odds of

Summary Points

- Large case-control studies have found an inverse correlation between dietary lignan intake and breast cancer risk.
- This study shows that increased intake of dietary lignans is inversely associated with breast cancer risk as well as improved prognostic characteristics in both premenopausal and postmenopausal women.
- The inverse correlation was most notable for ER⁻ tumors in premenopausal women.

having triple negative tumors compared to those in the lowest tertile (ER⁻, PR⁻, HER2⁻; OR 0.16 [95% CI 0.04-0.62]). This reduction was primarily associated with lariciresinol and pinoresinol.

COMMENTARY

The results of this ambitious study expand on previous epidemiological studies that have found an inverse correlation between dietary lignan intake and breast cancer risk (please note brief review below) by adding more detailed data on reduced risk of specific types of cancer as well as prognosis. Lignans are naturally occurring diphenoxy compounds that are classified as phytoestrogens.¹ Commonly found in whole grains, seeds, nuts, legumes, fruit, and vegetables, the highest concentrations are currently found in flaxseed powder extracts standardized to secoisolaricresinol and a 7-hydroxymatairesinol (HMR) powder extracted from the knot wood of Norwegian Spruce.^{1,2} The researchers report in the Discussion section of the paper that the primary sources of total lignans in the study population were apricots, broccoli, berries, coffee, and red wine. The primary sources of matairesinol intakes were onions, oranges, "salty snacks," peaches, and coffee. The primary sources of lariciresinol were broccoli, winter squash, berries, apricots, and coffee. Interestingly, they did not include flaxseed or tea in the list of foods or beverages.

Dietary lignans are converted by gut microflora to the mammalian lignans enterolactone (ENL) and enterodiol (END). Matairesinol and HMR are directly converted to ENL while pinoresinol, lariciresinol, and secoisolaricresinol are first converted END, which then partially converts to ENL.¹ One study found that sesame seeds, a rich source of matairesinol, more efficiently raised ENL levels when compared to flaxseed.³

Several, but not all, epidemiological studies have

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reported reduced risks of breast cancer associated with either increased intake of dietary lignans and/or higher blood levels of ENL.⁴ A case-control study of premenopausal women found that overall breast cancer risk was inversely correlated with plasma ENL.⁵ Another found an inverse correlation between breast cancer risk and plasma ENL in both premenopausal and postmenopausal women.⁶ Two additional studies found that increased plasma ENL was associated with a significant decrease in risk of ER⁻ breast cancer in premenopausal⁷ and postmenopausal women.⁸ Finally, in a large case-control study, higher dietary lignan intake and serum levels of ENL and END were associated with a significantly reduced risk of ER- and PR+ breast cancer in postmenopausal women.⁹

As pointed out by the authors of this new study, ER- tumors are more common among younger women and have a poorer prognosis because of fewer treatment options.¹⁰ While less common, triple negative breast cancer also has a poor prognosis due to lack of effective treatments. The identification of simple modifiable lifestyle changes such as increased lignan intake could potentially reduce the occurrence of less favorable tumor types, and perhaps

have a considerable impact toward reducing the burden of the disease in both premenopausal and postmenopausal women. ■

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CME QUESTIONS

1. The exact cause of menopausal hot flushes has been delineated.
 - a. True
 - b. False
2. In a case-control study looking at breast cancer risk and prognosis, dietary lignan intake was inversely correlated with the following in premenopausal women?
 - a. Grade 3 tumors
 - b. ER- breast cancer
 - c. Triple negative tumors
 - d. All of the above
3. Previous case-control studies have found an inverse correlation between breast cancer risk and plasma levels of the following mammalian lignan:
 - a. secoisolariciresinal .
 - b. genistein.
 - c. enterolactone.
 - d. pinoresinol.

[IN FUTURE ISSUES]

Fish consumption and colorectal cancer

Chocolate and cardiovascular disease

The science behind fad diets

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