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OBESITY

Low-Carbohydrate Diets and Weight Loss

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Dr. O'Mathúna and Ms. Feeney report no financial relationships relevant to this field of study.

The incidence of obesity continues to rise. According to the World Health Organization, 1.5 billion people are overweight, with 300 million obese.[1] About two-thirds of the U.S. population is overweight, with one-third being obese.[2] The number of overweight children in the world more than doubled between 2005 and 2010.[3] Obesity is a major risk factor for chronic illnesses, particularly type 2 diabetes, cardiovascular diseases, and some cancers.

In response, various weight-loss strategies have been proposed, popularized, and researched. Low-carbohydrate diets (LCD), while varying in their details, advocate reducing carbohydrate intake while increasing protein calories. The Atkins diet is the most popular of these, with similar principles underlying the Carbohydrate Addict's and Sugar Busters diets.[4] Controversy exists over their effectiveness and safety, especially for long-term weight loss.[3] With so many people shunning carbohydrates and loading up on protein, evidence from recent studies will be reviewed here so that practitioners can advise patients seeking to lose weight.

BACKGROUND

Evaluating LCD is challenging because many different approaches are recommended. Even in reports of clinical trials, it can be difficult to identify participant consumption. Most commonly, the diets are described based on the percent of each macronutrient. Figure 1 shows common diets presented this way. Such representations fail to identify the total number of calories consumed. In some cases, these diets have no restrictions on protein or fat.

Another approach to classifying LCD uses the absolute amount of carbohydrates. According to one scheme, very low carbohydrate diets restrict carbohydrate intake to < 20 g/d, and LCD to < 60

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g/d,[5] although other quantities are used.[6] The average American diet now includes a higher proportion of carbohydrates than in previous generations. The average U.S. male consumes 300 g/d carbohydrates, compared to a recommended daily allowance of 130 g/d.[7]

Conventional dieting advice has recommended reducing calories and the proportion of fat, especially saturated fat. The Atkins diet was one of the first popular diets to recommend reducing carbohydrates while eating unrestricted amounts of high-protein, high-fat foods like meat, eggs, fish, cheese, olives, and nuts. After an initial 2-week induction period, small amounts of complex carbohydrates are allowed (primarily vegetables and fruits), but breads, pastas, and starchy foods are off limits. The goal is carbohydrate intake below 20 g/d.[4] Part of Atkins' argument was that even while Americans were decreasing dietary fat from 40% to 32%, obesity became highly problematic.[8] However, while the percentage of fat consumed has decreased since 1975, per capita fat consumption increased by 10 pounds per year, and consumption of simple carbohydrates (like sugar, syrup, and processed flour and rice) increased by 20 pounds per year.[9] Clearly, the obesity problem is more complex than some promoters of various diets suggest, with the types of food available and exercise levels also being crucial factors.

MECHANISM OF ACTION

A number of metabolic processes are believed to contribute to LCD weight loss. Severely restricting carbohydrates causes glycogen stores to deplete. Each gram of glycogen is stored along with 3 g of associated water, which contributes to weight loss.[3] Fewer serum carbohydrates leads to a lower insulin/glycogen ratio, which triggers fatty acid oxidation and ketone body production. The resulting ketosis (not to be confused with ketoacidosis) leads to ketone bodies being metabolized to provide energy for essential organs such as the brain, kidneys, and heart.[3] Ketosis has been hypothesized to suppress appetite and promote thermogenic energy expenditure. Fatty acid oxidation may lead to weight loss as fat is metabolized. High-protein diets also may help people feel full quicker and for longer, thus reducing overeating and snacking. However, elevated serum fatty acid levels may also increase cardiovascular disease risk, insulin resistance, and liver steatosis.

CLINICAL STUDIES

Many studies have been conducted on LCD for weight loss, although most are not randomized controlled trials (RCT). The most recent systematic review was published in August 2012.[1] Seventeen RCTs were identified that lasted at least 3 months. Studies involving subjects with diabetes, cancer, epilepsy, or other diseases were excluded as the reviewers focused on healthy people seeking weight loss. The included studies had a variety of control diets in the comparison groups, and some controlled the total calorie intake and some did not. To avoid complications from these variations, a meta-analysis was conducted using only before and after data from the LCD groups. Significant weight loss compared to baseline was identified at various intervals. At 6 months, mean weight loss was 6.82 kg (95% confidence interval [CI], -7.03 to -6.61); for 6-11 months, -8.09 kg (95% CI, -8.38 to -7.79); for 12-23 months, -6.33 kg (95% CI, -6.87 to -5.79); and at 24 months, -4.65 kg (95% CI, -5.37 to -3.93). However, the reviewers noted that the long-term effectiveness remains unclear as only two studies had follow-up assessments at 24 months. Cardiovascular risk factors also were found to change positively, including significant reductions in blood pressure, plasma triglycerides, blood glucose and plasma insulin, and increased high-density lipoprotein cholesterol (HDL-C).

Earlier systematic reviews compared the effectiveness of LCD with other diets, particularly low-fat diets (LFD). One published in 2009 identified 13 such RCTs lasting at least 6 months.[5] After 6 months, weight loss with LCD was significantly greater than with LFD (-4.02 kg; $P < 0.00001$). At 12 months, the difference had fallen to -1.05 kg ($P < 0.05$). The dropout rate across all these studies was 36%, with significantly greater attrition from the LFD (P =

Summary Points

- Low-carbohydrate diets continue to be popular among those seeking to lose weight.
- Evidence shows that low-carbohydrate diets are more effective than low-fat diets over 6 months and possibly 12 months.
- Evidence is lacking for the long-term effectiveness of low-carbohydrate diets, primarily due to a lack of longer studies.
- The long-term use of low-carbohydrate diets may elevate some cardiovascular risks for some people, but more research is needed to clarify this.

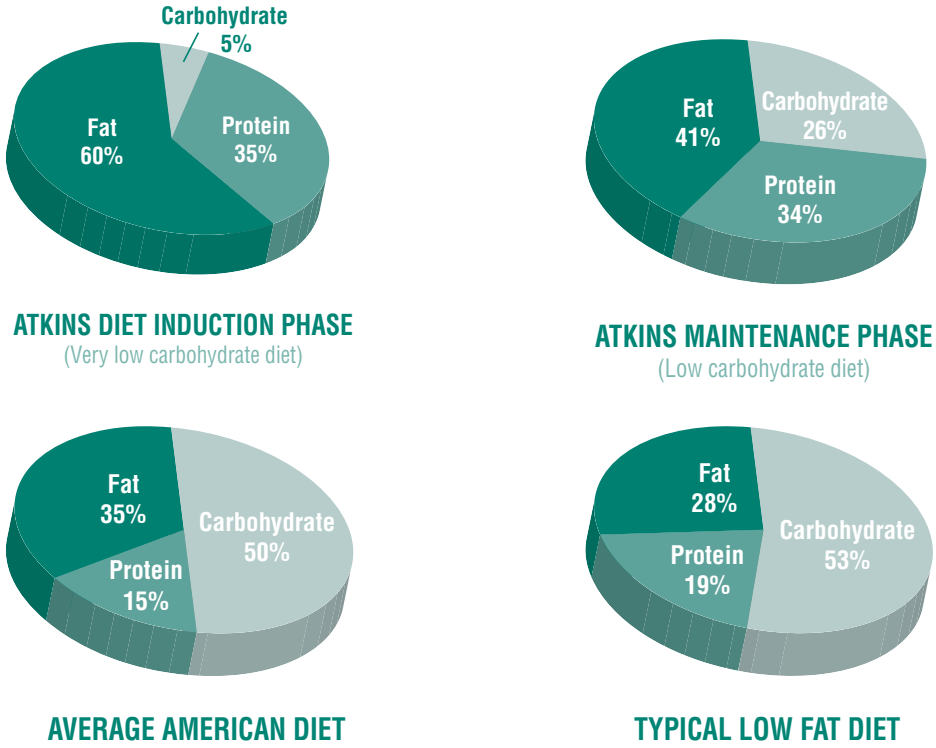
0.001). One study lasted 36 months, at which point the two groups did not differ significantly. Between 6 and 36 months, the low-fat group did not change weight, while those on LCD regained weight to a non-significant degree. Total cholesterol was significantly higher with LCD after 6 months (0.19 mmol/L; $P < 0.0001$), but not after 12 months (0.10 mmol/L; $P = 0.31$). Low-density lipoprotein cholesterol (LDL-C) was significantly higher with LCD after 6 months (0.14 mmol/L; $P < 0.00001$) and even higher after 12 months (0.37 mmol/L; $P < 0.00001$). HDL-C was significantly higher with LCD after 6 months (0.04 mmol/L; $P = 0.03$) and higher after 12 months (0.06 mmol/L; $P < 0.05$).

An earlier systematic review identified five trials involving subjects with a body mass index of at least 25.[10] This meta-analysis found significantly more weight loss with LCD than LFD at 6 months (-3.3 kg; 95% CI, -5.3 to -1.4) but not at 12 months (-1.0 kg; 95% CI, -3.5 to +1.5). Similar results to the more recent systematic review were noted for serum lipid levels: LCD led to more favorable changes in triglyceride and HDL-C levels, with less favorable changes in total cholesterol and LDL-C levels. The lipid outcomes were similar after 6 and 12 months.

ADVERSE EFFECTS

Short-term adverse effects are relatively common with LCD, though these are usually transient and not serious. In a study funded by the Atkins Center, among those using the Atkins diet for 6 months, 70% were constipated, 65% had halitosis, 54%

Figure 1. Comparison of Atkins Diet Induction Phase with Maintenance Phase, the Average American Diet, and a Standard Low-fat Diet[11]



had headaches, and 10% had hair loss.[12] Reduced fruit, vegetable, and whole-grain consumption may explain these effects.

Much of the controversy about LCD arises from concerns about long-term adverse effects. These center around their high fat content and potentially low plant and fiber content. Additional dietary protein often comes from animal sources that are high in saturated fat and cholesterol. For example, in one study, people consuming the Atkins diet increased their cholesterol intake from 215 mg to 461 mg and then to 285 mg (at baseline, 3 months, and 6 months, respectively).[13] These levels were significantly higher than those on the conventional diet: 273 mg, 169 mg, and 182 mg, respectively ($P \leq 0.05$).

The impact of elevated cholesterol intake is seen in the serum lipid changes identified in RCTs and systematic reviews discussed above. Although beneficial changes are found in total triglyceride and HDL-C levels, changes that increase cardiovascular risk are found for total cholesterol and LDL-C levels. The overall change and direction of risk with these effects is debated.[6] The U.S. Nurses' Health Study found no association between LCD and coronary heart disease risk.[14] In contrast, three small European studies showed some association, leading to an extensive cohort study of more than 43,000 Swedish women monitored for 15 years.[15] This found that for every 10% decrease in carbohydrate intake or increase in protein intake, the risk of cardiovascular disease increased by 5%, which was statistically significant.

A cross-sectional study of 247 patients with elevated cardiovascular risks examined the impact of LCD on arterial wall function.[16] A scoring tool quantified the macronutrient percentages with the lowest quartile scores corresponding to 45% carbohydrate, 20% protein, and 32% fat. The highest quartile scores were diets containing 29% carbohydrate, 24% protein, and 40% fat. Those with the highest scores (lowest carbohydrate) had significantly higher arterial vascular reactivity as measured by peripheral arterial tonometry ($P = 0.037$). This association was strongest in patients with type 2 diabetes or metabolic syndrome, and was independent of common confounding factors. Such negative effects on endothelial function have been demonstrated in a few other studies. A cohort study of more than 40,000 men followed for 20 years found that LCD was associated with increased risk of type 2 diabetes ($P < 0.01$).[17]

CONCLUSION

Controlled studies of LCD support its greater effectiveness than LFD over 6 months and, possibly, over 12 months. Very few studies last longer than 12 months, but the evidence suggests that long-term weight loss is difficult to sustain. During LCD, changes in the lipid profile are conflicting (but mostly beneficial for triglycerides and fasting insulin), making clear conclusions difficult. However, cohort studies have revealed associations between cardiovascular disease risks and long-term LCD that must be taken seriously.

Part of the difficulty in assessing LCD comes from their many variations. As carbohydrates are restricted, protein and fat portions are increased, but often in different ways. Animal sources will lead to increased consumption of saturated fat and cholesterol, but plant sources can be used instead. Protein can be obtained from lower-fat meats (such as chicken or turkey) and vegetable sources to minimize the proportion of saturated fat (see *Harvard HEALTHbeat*[18] for some specific examples). Fruit and vegetable consumption is sometimes curtailed as a way of avoiding carbohydrates; this may lead to insufficient vitamins being consumed and the need for vitamin supplementation.[3]

RECOMMENDATION

Current evidence supports the use of LCD for weight loss up to about a year. Beyond this, they appear to be no more effective than conventional, low-fat, reduced-calorie diets, but LCDs are significantly more effective than those diets for insulin resistance and related conditions; hence, there may be a subset of patients for which this diet is important to consider. This may be due to the difficulty of sustained adherence to these diets. At the same time, constipation and headaches are common, and may lead to discouragement in their use. In addition, the long-term nutritional quality of LCDs, and their impact on cardiovascular risk factors, is a major concern.

Diet recommendations should be individualized and take account of total calorie consumption, exercise, and availability of personal support. Those already at higher risk for cardiovascular disease should be more cautious about LCDs. At the same time, the risk from these diets may be less than from obesity itself. For those who are generally healthy and seeking shorter-term weight loss, LCD may be an effective strategy at least in the short-term. ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

A 'Check' in the 'Fish Oil Doesn't Work' Column: Results from a Meta-analysis

By David Kiefer, MD

SYNOPSIS: A meta-analysis of 20 human randomized, controlled clinical trials of at least 1 year in duration found that there was no relationship between diet or supplement-derived omega-3 supplementation and cardiovascular disease outcomes.

SOURCE: Rizos EC, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. *JAMA* 2012;308:1024-1033.

The authors of this trial were interested in clarifying the use of marine-derived omega-3 (n-3) polyunsaturated fatty acids (PUFAs) for cardiovascular protection, recognizing that there are conflicting results in the medical literature on the topic. The overall goal was to determine the association between n-3 PUFAs and "major patient-oriented cardiovascular outcomes."

The authors included any randomized clinical trial involving n-3 PUFA supplementation in adults, including supplementation that was either from diet or supplements. The trials had to have a control (another diet or placebo), involved primary or secondary cardiovascular disease (CVD) prevention, and could have any of a number of outcomes, such as all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke. The trials had to be at least 1 year in duration.

All of the typical databases (i.e., PubMed, EMBASE) were searched, and the trials were assessed for risk of bias using a modification of the Cochrane collaboration tool. The authors separately analyzed the data from trials where the n-3 PUFAs were obtained from diet vs supplements, and for each of the major CVD outcomes, calculating relative risks (RR), absolute risk reductions (ARR), and 95% confidence intervals (CI). In addition, the omega-3 dose was considered as a continuous variable.

Twenty clinical trials, with a median duration of 2 years and mostly considered "high quality," were included out of 3635 citations originally found in their search mechanism; these 20 trials included data on 68,680 patients, and documented 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. Two of the 20 trials involved dietary counseling to achieve the n-3 PUFA intervention, while the other 18 used supplements. The mean total n-3 dose was 1.51 grams daily, which included 0.77 grams daily of

Summary Points

- A meta-analysis of 20 studies seems to indicate that marine omega-3 PUFA intake does not lower the risk of major cardiovascular outcomes.
- Although it was a large and well-done meta-analysis, there were two issues that may complicate clinical applicability: The omega-3 dose varied significantly among the trials and the mean omega-3 dose was 1.51 grams total fish oil, arguably lower than what has been shown to have a physiological effect, such as on lowering triglycerides.

eicosapentaenoic acid (EPA) and 0.60 grams daily of docosahexaenoic acid (DHA).

The two trials that used a dietary intervention examined secondary prevention of CVD and were done by the same European research group. Each trial aimed for an n-3 PUFA intake of about 1 gram daily and compared the intervention to a non-fish oil diet. The results showed both benefits for n-3 supplementation and benefits for the control groups, some of which were statistically significant. Because of this discrepancy, which was difficult to explain given the research methods as described in the trials, the authors of the review decided not to include these results in the final analysis.

For the trials that used fish oil supplementation as the n-3 PUFA source, there was no observed reduction in all-cause mortality (RR, 0.96; CI, 0.91-1.02), and, interestingly, the researchers found that more recent research refuted earlier benefits, accounting for the overall lack of documented effect. Similarly, there was not an association between n-3 PUFAs and improvements in the other parameters, minus one: for cardiac death, there was a slight reduction in risk (RR, 0.91; CI, 0.85-0.98), though the researchers claimed that the improvement disappeared after correction for multiple comparisons.

COMMENTARY

Although there is accumulating evidence for the use of n-3 PUFAs in mood disorders and inflammatory conditions, the cardiovascular system is probably the most well-known site of physiological activity and benefit for n-3 PUFAs; we are all familiar with the published trials on dietary fish consumption or fish oil supplementation and the morbidity and mortality related to cardiovascular conditions such as coronary artery disease, arrhythmias, heart failure, and hypertension.[1,2,3,4,5] Most experts recommend two servings of fish weekly for primary CVD prevention, and 1000 milligrams of EPA + DHA supplementation daily for secondary CVD prevention,[3] though, as the authors of this meta-analysis point out, there is controversy about efficacy in many of these diagnoses. What does seem to be well-accepted is the positive effect of n-3 PUFAs on hypertriglyceridemia (approximately 2-4 grams of EPA + DHA daily).[2,6,7]

So, how do we put this all together in the context of the current meta-analysis, where none of the CVD outcomes showed a benefit associated with n-3 intake? The authors themselves state that the individual trials might be underpowered to detect a small effect, which would lead to a meta-analysis also unable to show benefits to n-3 PUFA supplementation. Also, there is the issue of dose. The mean n-3 PUFA intake for the 20 trials is lower than what we know would account for an appreciable effect on triglycerides, probably the most convincing physiological effect that would have a tangible benefit. The authors did analyze the n-3 dose variably and failed to find significant effects on the CVD outcomes examined. It is unclear whether interstudy n-3 dose variability would be given due justice in the analysis presented here. Such a nuance, and an important one clinically, might be lost. Furthermore, we do not know about baseline values for triglycerides (or many other relevant variables) for most of the trials in this meta-analysis, clearly an important issue and one that reminds us how distant a meta-analysis is from our one-on-one interactions with patients in clinic. An individual may decide, for instance, that, given the low possibility for adverse effects with n-3 PUFAs, they would like to continue their daily "slug" of fish oil anyway, awaiting, as we all are, further clarification of this issue from researchers.

So, there are some shortcomings that might explain why past n-3 research was not validated in this meta-analysis. That said, the researchers bring several strengths to the literature on n-3 PUFAs. Not only is the quantity of patients (and trials originally reviewed) that were included in this meta-analysis impressive, but the authors provide an interesting chronological perspective about n-3 clinical trials, namely that perhaps the more recent trials are trumping the older published research by showing primarily neutral CVD effects.

Perhaps we are starting to learn, via this meta-analysis and other recent research, that n-3 PUFAs

aren't a cure-all, standalone treatment for serious CVD. It will likely remain a part of an integrative approach to CVD, together with lifestyle change, dietary modifications, and a handful of supplements and pharmaceuticals. Hopefully, future work will address some of the pitfalls and gaps alluded to here, and add to these results. ■

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BONE HEALTH

ABSTRACT AND COMMENTARY

Vitamin E and Bone Health — The Alpha and the Gamma

By Donald J. Brown, ND

Managing Director, Natural Product Research Consultants, Seattle, WA

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

SYNOPSIS: Alpha-tocopherol is the primary form of vitamin E used in dietary supplements. The results from this study suggest that supplementation with alpha-tocopherol by postmenopausal women may reduce serum gamma-tocopherol levels and negatively impact bone formation.

SOURCE: Hamidi MS, et al. Effects of vitamin E on bone turnover markers among U.S. postmenopausal women. *J Bone Mineral Res* 2012;27:1368-1380.

Using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002, the researchers examined the association between dietary and total (diet and supplements) alpha-tocopherol intake, serum alpha-tocopherol and gamma-tocopherol levels and their ratio, and bone turnover markers (BTMs) among postmenopausal women aged ≥ 45 years. Adjusting for relevant confounders (e.g., ethnicity, nicotine exposure, central adiposity, dietary supplement use in the past month, and total cholesterol and triglycerides), the association between intake and serum levels of tocopherols and serum bone-specific alkaline phosphatase (BAP) and urinary N-teleopeptides/creatinine (uNTx/CR) were measured. BAP is a biomarker of bone formation and uNTx/Cr is a biomarker of bone resorption. The study sample included 497 postmenopausal women (mean age 65.5 ± 0.6 years) who were not taking estrogen, steroids, or osteoporosis medications, and were free from kidney and liver disease, cancer, and rheumatoid arthritis. All subjects were fasting for > 9 hours prior to a visit where they completed a 24-hour dietary recall and a questionnaire regarding daily intake of alpha-tocopherol from dietary supplements. Respondents were classified as vitamin E supplement users if they reported using supplements at least 15 times in the previous 30 days. Data for gamma-tocopherol were not available. Fasting serum samples were collected on the examination day and used to measure alpha-tocopherol and gamma-tocopherol. BTMs also were measured during the examination.

More than 45% of the subjects had used vitamin E (alpha-tocopherol) supplements in the past month. Among those who used dietary supplements, 81.4% consumed a supplement that contained alpha-tocopherol; other forms of vitamin E were not documented. Of those women, 39.4% had intakes > 400 IU. The average daily intake of alpha-tocopherol from supplements ranged from 6.7-1188 IU, with a median intake of 90.64 IU. Vitamin E supplement users had significantly lower serum gamma-tocopherol, higher serum alpha-tocopherol, and a higher ratio of serum alpha-tocopherol to gamma-tocopherol than non-users. High total alpha-tocopherol and serum alpha-tocopherol were associated with decreased BAP levels in the

Summary Points

- The predominant form of vitamin E used in dietary supplements is alpha-tocopherol.
- In doses of 400-1200 IU/day, alpha-tocopherol has been shown to decrease serum levels of gamma-tocopherol.
- The results of this study confirm the above and also suggest that reduced serum levels of gamma-tocopherol may negatively impact bone formation in postmenopausal women.

unadjusted analysis, but not in the analysis adjusted for potential confounders. Conversely, high serum gamma-tocopherol levels and a low ratio of serum alpha-tocopherol to gamma-tocopherol were associated with increased BAP levels ($P < 0.01$ for both). There were no associations between any of the vitamin E variables and uNTx/Cr.

COMMENTARY

Alpha-tocopherol and gamma-tocopherol are the two predominant isomers of vitamin E in the human body and diet, respectively. The other two isomers are beta-tocopherol and delta-tocopherol. Gamma-tocopherol comprises about 70% of the vitamin E in the typical American diet and is found in high levels in the commonly ingested soybean oil. Although alpha-tocopherol has higher antioxidant activity, gamma-tocopherol has superior anti-inflammatory properties.[1,2] The predominant form of vitamin E used in dietary supplements, alpha-tocopherol in doses 400-1,200 IU/day, has been shown to decrease serum levels of gamma-tocopherol by accelerating its metabolism.[3,4] Some experts have suggested that some of the adverse effects attributed to long-term vitamin E supplementation may be due alpha-tocopherol's depletion of gamma-tocopherol.[5]

The findings of this study may add further fuel to concerns about alpha-tocopherol supplementation and the depletion of gamma-tocopherol. As noted by the researchers, the results of this study, as well as in vitro and animal studies, lead to the hypothesis that gamma-tocopherol may uncouple bone turnover, resulting in increased bone formation without affecting bone resorption. In short, postmenopausal women taking vitamin E supplements in the form of alpha-tocopherol may be negatively impacting bone formation.

The Women's Health Initiative also examined the relationship between vitamin E intake, serum alpha-tocopherol and gamma-tocopherol, and bone health in postmenopausal women.[6] The study found no association between tocopherols and bone mineral density (BMD). It is interesting to note that serum tocopherols reflect short-term dietary intake, while BMD is affected by long-term dietary intake. The decision to use BTMs better matches changes in bone formation and resorption with changes in serum tocopherol levels.

The researchers point out several limitations to their study. Due to the cross-sectional design, a causal relationship between vitamin E and BTM levels could not be determined. Also, they correctly point out that people consume foods and often multiple dietary supplements, not single nutrients. This may make the association between any single nutrient or select number of nutrients with disease outcomes incorrect because of residual confounding. Finally, intake of gamma-tocopherol was not available for NHANES 1999-2002.

A small handful of nutritional experts have advocated for the use of vitamin E supplements that offer mixed tocopherols with at least 50-100 IU of gamma-tocopherol per 400 IU of D-alpha-tocopherol.[7] Although further research is needed to more clearly identify the role that gamma-tocopherol may play in bone formation, it may be time to heed this advice when recommending vitamin E supplements. ■

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ABSTRACT AND COMMENTARY

Meditation and Exercise vs Common Cold — An Ounce of Prevention and Pound of Cure?

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

SYNOPSIS: Meditation and exercise interventions were shown to reduce the frequency, duration, and symptom severity of acute respiratory illness in adults aged 50 and older compared to a waitlist control group.

SOURCE: Barrett B, et al. Meditation or exercise for preventing acute respiratory infection: A randomized controlled trial. *Ann Fam Med* 2012;10:337-346.

Non-influenza acute respiratory infection (ARI) is common, costly, and often debilitating. In research published in 2003, Fendrick et al estimated 500 million episodes of ARI per year in adults and children, with a total economic impact of $40 billion annually. Direct costs, estimated at $17 billion per year, included physician visits, laboratory costs, OTC medication use, and prescriptions. An estimated $22.5 billion in indirect costs were due to missed work days resulting from personal illness or providing care at home for a sick child.[1] In a summary of mindfulness research, Greeson reported evidence that mindfulness training reduces negative emotion and perceived stress, both of which have been linked to increases in self-reported illness as well as viral shedding and elevated biomarkers of inflammation. In addition, mindfulness training has shown positive influence on antibody responses to influenza vaccine, reduced cortical levels in cancer patients, and trends toward normalized immune function in cancer and HIV patients.[2] Epidemiological evidence suggests that moderate habitual exercise is associated with a 29% reduction in risk of succumbing to an upper respiratory tract infection compared to sedentary lifestyle.[3] Based on existing evidence, Barrett et al designed this study to more robustly test the hypothesis that mindfulness meditation or moderate intensity exercise could reduce ARI incidence, duration, and severity.

A total of 154 adult participants were selected after community recruitment and screening, and randomly assigned to one of two active treatment groups or an observational control group. The active interventions consisted of either an 8-week mindfulness meditation course or an 8-week exercise program. The two interventions were matched in terms of total group contact time (eight 2½ hour weekly sessions), recommended home practice time (45 minutes per day), and location. The meditation intervention was based on the mindfulness-based stress reduction (MBSR) course created by Jon Kabat-Zinn at the University of Massachusetts,[4] and all of the MBSR instructors were trained by Kabat-Zinn's group. The exercise program was designed by the physiology staff at the UW Health Sports Medicine Center and supervised by three licensed and experienced athletic trainers. The exercise program consisted of moderate-intensity sustained aerobic exercise using exercise equipment in the center or via brisk walking or jogging at home, approximately 420 minutes of exercise per week. Control group participants were offered meditation or exercise training, or a monetary equivalent at the end of the trial, which started in September and finished in May the following year.

The primary outcome was global severity for all ARI illness days from the time of consent until study exit, as measured by the Wisconsin Upper Respiratory Symptom Survey (WURSS-24), a validated instrument for assessing ARI symptom severity. To determine if a participant had an ARI during the study period, he or she had to meet predetermined criteria about number, severity, and duration of symptoms on questionnaires and the WURSS that had been distributed at the time of enrollment. All participants were contacted by telephone twice weekly starting post-intervention until the close of the study period to remind them to begin documenting ARI symptoms on these questionnaires as soon as they believed they might be getting a cold. Daily severity scores were collected as well as illness duration. Secondary outcome measures included scores on a variety of validated measures of self-reported physical and mental health, stress levels, exercise, and mindfulness. Missed days of work or school were documented as well as health care visits; however, use of OTC or prescription medications

Summary Points

- Because of high incidence, acute respiratory illness (ARI) ranks number one in the top 10 most expensive illnesses.
- Previous research has suggested that enhancing general physical and mental health may reduce ARI burden.
- In this study, 8-week training in meditation or moderate exercise substantially reduced severity and number of illness days compared to an observational control group over one winter-spring cold and flu season.

was not documented. In addition, a nasal wash was collected from all participants who developed ARI within 3 days of symptom onset and was analyzed for interleukin-8 and neutrophil count, markers for inflammation. Viral nucleic acid was analyzed for virus identification.

Of 154 participants, 82% were female, 94% were white, and the mean age was 59.3 years. One hundred forty-nine (96.7%) completed the trial. In the meditation group, there were 27 ARI episodes and 257 days of illness, and in the exercise group, there were 26 ARI episodes and 241 days of illness. The control group experienced 40 ARI episodes and 453 days of illness. Mean global severity scores were 144 for meditation, 248 for exercise, and 358 for control. The researchers chose $P \leq 0.025$ as the cutoff for null hypothesis rejection to control for multiple testing, because increasing the number of tests performed on a study sample also increases the probability that any given test will yield misleading results that appear to be significant, but are not actually so. Thus, these values trended toward statistical significance compared to controls in number of illness days in the meditation group ($P = 0.034$) and exercise group ($P = 0.032$). Global severity scores were significantly lower for the meditation group compared to controls ($P = 0.004$), though not for the exercise group ($P = 0.16$). ARI-related missed days of work were significantly lower in the meditation group compared to the control group ($P < 0.001$) and trended toward statistical significance in the exercise group ($P = 0.041$). Nasal washings yielded similar results for all groups in terms of frequency and types of viruses isolated. Biomarkers for inflammation were similar in all groups except for slightly higher IL-8 levels in meditation participants.

COMMENTARY

This study incidentally helps illustrate one of the problems with *P* values in clinical research. Though they are essential for helping to discern that the differences observed between groups are not solely due to chance, they don't tell us enough about measured effect sizes and the clinical significance of any differences between groups, parameters that must be examined and interpreted independently. Despite the fact that this study sample was not large enough to yield statistically significant *P* values for some outcomes, the size of the differences (effect sizes) in reduction of ARI illness in the treatment groups compared to controls was impressive and appears clinically significant. Incidence, duration, and global severity of ARI were 29%, 43%, and 31% lower in the exercise group and 33%, 43%, and 60% lower in the meditation group compared to controls. These differences and reported trends toward reduced ARI-related work absenteeism in this study suggest a clinically meaningful impact on ARI in terms of suffering and cost.

The treatment groups were divided into two cohorts, one group starting intervention at the beginning of the cold season in September (n = 94) and the other starting the following January (n = 60). Study exit was the following May; thus, the January groups were not followed through a complete winter-spring cold and influenza season, somewhat limiting interpretation of results. Due to the nature of the behavioral interventions, participants could not be blinded to their treatments and might be subject to self-reporting bias. However, the authors argue that self-report bias is unlikely, given the fact that scores on the secondary outcome measures of self-reported psychosocial health really showed no improvement over the course of the study. There was no control for group effect, the influence that merely participating in a group activity may have on outcomes, as the control group was observational and did not meet at any time as a group during the study. Furthermore, being predominantly female and white, the study sample was not representative of the U.S. population.

Nonetheless, this is an impressively and carefully designed study with intriguing results. This is the first randomized control study to assess the effects of mindfulness meditation training on ARI, the first to use a validated outcome measure to assess effects of exercise on ARI, and the first to compare two active intervention groups with an observational control. The biometric measures of inflammatory markers and viral identification are an additional strength. Addressing the limitations in this study in future research is urgently needed because of the potential public health impact of reducing the

suffering and costs from ARI implied in this study. Both mindfulness meditation practice and exercise have multiple documented physical and mental health benefits with few risks. Though we are far from incorporating meditation and exercise into clinical guidelines for ARI prevention based on current research, mentioning these interventions as potentially helpful for adult patients predisposed to respiratory infections can certainly be encouraged while awaiting further research data. ■

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4. Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain and Illness*. New York, NY: Bantam Dell; 1990.

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Upon completion of this educational activity, participants should be able to:

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

CME QUESTIONS

1. Evidence from controlled clinical trials has found that low-carbohydrate diets are:
a. effective for weight loss over shorter-term periods (up to 6 or 12 months).
b. effective for weight loss in the long term (more than 2 years).
c. ineffective for weight loss.
d. an unsafe strategy for anyone pursuing weight loss.

2. Low-carbohydrate diets are believed to help people lose weight by:
a. putting people's metabolism into ketosis.
b. reducing people's appetite through a sensation of being full.
c. fatty acid oxidation leading to depletion of fat stores.
d. All of the above

3. The most common low-carbohydrate diets recommend that protein be consumed:
a. in highly restricted portions.
b. to as large an extent as dieters wish.
c. in smaller portions in proportion to the reduction in carbohydrates.
d. to the same extent as it was prior to beginning the diet.

4. According to the most recent meta-analysis as reviewed in this issue, when omega-3 fatty acid supplementation (either dietary or supplement) is studied, there are convincing improvements in the relative risk of:
a. cardiac death.
b. myocardial infarction.
c. stroke.
d. All of the above
e. None of the above

5. In the reviewed study, vitamin E supplement users were found to have:
a. a higher ratio of serum alpha-tocopherol to gamma-tocopherol.
b. lower serum levels of gamma-tocopherol.
c. higher serum levels of delta-tocopherol.
d. Both A and B
e. None of the above

6. Higher serum gamma-tocopherol was associated with higher serum levels of which marker of bone formation?
a. N-teleopeptides/creatinine
b. Bone-specific alkaline phosphatase
c. Serum calcium
d. None of the above

7. In the study of meditation or exercise for reducing acute respiratory illness burden, which of the following is true about design and results?
a. There was a high drop-out rate.
b. The participants were not representative of the general population.
c. Children were included in the study.
d. Neither meditation nor exercise statistically influenced outcomes.

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