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INSOMNIA

ABSTRACT & COMMENTARY

Lettuce for Sleep? Maybe, but Not in Salad Form

By David Kiefer, MD, Editor

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

SYNOPSIS: The authors of this single-blind randomized study found that 1,000 mg of culinary lettuce seed nightly for two weeks can improve sleep in pregnant women with insomnia.

SOURCE: Pour ZS, Hosseinkhani A, Asadi N, et al. Double-blind randomized placebo-controlled trial on efficacy and safety of *Lactuca sativa* L. seeds on pregnancy-related insomnia. *J Ethnopharmacol* 2018;227:176-180.

For obvious reasons (think teratogens or abortifacients), clinicians are wary about prescribing anything for the myriad of conditions that can accompany pregnancy. These Iranian researchers are filling a void in such options for pregnant women by exploring one specific herbal medicine for insomnia. The researchers provided significant background about traditional Iranian medicine, within which is a robust history of herbal medicine use. One such plant, called khas or lettuce (*Lactuca sativa*, Family Asteraceae), and the seeds and the seed oil have a history of use as a sedative in general and for pregnancy. This is indeed the same culinary lettuce of which the leaves are a common part of salads in many cultures.

One hundred pregnant women with insomnia were included in this prospective, randomized, controlled trial. The participants needed to have a score of > 5 on the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-administered

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Summary Points

- One hundred pregnant women with insomnia were randomized to receive one capsule nightly of lettuce seed (1,000 mg) or placebo for two weeks.
- Only 35 women in each group completed the trial; those in the lettuce group had statistically significant improvement in sleep ($P = 0.021$).
- The lettuce species (*Lactuca sativa*) used is different than the wild lettuce species (*Lactuca virosa*) available as an herbal medicine in the United States.

questionnaire that assesses seven areas (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction). Each area is rated from 0 to 3, and a lower score indicates better sleep. The researchers excluded women with a body mass index > 30 kg/m^2 or a history of sleep disorders before pregnancy, mood disorders, gestational diabetes mellitus, drug abuse, or hypertension (including pre-eclampsia), as well as vague conditions such as "fetal disorder" or "history of chronic somatic disease."

The women were randomized to 1,000 mg of lettuce seed nightly for two weeks (n = 50) or matched placebo containing corn starch (n = 50). This appeared to be a single-blind study; only the women were unaware of the group to which they were assigned. To obtain the product for use in the study, the researchers purchased "plant samples" (presumably seeds) in a local market, confirming the identification by using the herbarium of the Faculty of Pharmacy at Shiraz University of Medical Sciences. The seeds also were cold pressed to determine the seed oil content.

Only 35 women in each group completed the study. Reasons for lack of completion included stopping the treatment or being lost to follow-up. It is unclear whether an intention-to-treat analysis was used for the final statistical analysis.

Table 1 shows the results of the lettuce seed and placebo on the sleep scores. Overall, the intervention led to a statistically significant improvement in overall sleep as demonstrated by a lower PSQI ($P = 0.021$).

The researchers did not find any adverse effects in the women attributable to the intervention. One fetal death occurred in a woman assigned to the lettuce seed group at an estimated gestational age of 29 weeks due to placenta previa, but this was not thought to be caused by the lettuce seed. They documented three adverse neonatal outcomes in the treatment group (two sepsis and one transient tachypnea of the newborn) and one in the placebo group (sepsis). Again, none were considered a treatment effect nor significantly different from typical community disease incidences.

■ COMMENTARY

There are scant scientific data upon which to draw and assess the results presented here. Yes, lettuce is a common culinary plant, but the use of this

Table 1: Results of Lettuce Seed and Placebo on Sleep Scores

	Mean PSQI Baseline	Mean PSQI After Intervention
Lettuce seed capsule	12.51	6.86
Placebo capsule	12.34	8.54

PSQI: Pittsburgh Sleep Quality Index

species as a medicine does not enter into the Western herbal conversation regularly, if at all. Wild lettuce (*Lactuca virosa*) occasionally is mentioned as a sedative, using the leaves and/or latex.[1,2] Furthermore, it is unclear whether the seeds or seed oil would have the same effects as the leaves or latex. That said, in their introduction, Pour et al weaved in traditional use data (often the start of the investigation of plant medicines) and mentioned an animal model that corroborated sedative properties. Also, as per another reference in the paper, the seed oil fatty acid profile has been elucidated; the relevance to insomnia and sedation remains to be explained.

The study itself was well-organized, and the results simple enough to understand and follow. It could have been made more rigorous by also blinding the pharmacist who prepared the treatments and placebos (making it "double-blinded"). Also, the significant dropout rate could have been addressed more convincingly by using intention-to-treat analyses. As is, it is entirely plausible that study dropouts did so because of untoward side effects, or, alternatively, because their insomnia was cured miraculously and they did not need any more treatment. We would not know given the approach to data analysis in this paper.

Is this research important to clinicians in the United States? A qualified yes. There are still compelling reasons to explore traditional herbal remedies for safe and effective treatments for a variety of medical conditions. Lettuce seeds in Asia have this traditional use, but information is necessary before they can be a part of a clinician's toolbox. Mechanistic studies, perhaps animal models, and certainly clinical research are important in this regard. This study begins that process, but it needs to be improved and expanded to include more participants in rigorous clinical trials. Lettuce seed *might* improve insomnia and it *might* be safe; we just do not know enough yet. Furthermore, anyone can buy garden lettuce seeds and make their own medicine, provided it is determined that is the best form for this herbal medicine. However, a quick search found a dearth of actual sedative herbal medicines based on this species; the preponderance of products available were for wild lettuce. In conclusion, this is an interesting herbal treatment for a demographic without many current options, and there is a tradition of use outside of the United States. More basic science and clinical work, and then adequate sources and products, are necessary before this can be recommended confidently. ■

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OBESITY

ABSTRACT & COMMENTARY

Weight Loss Maintenance — Is Low-Carb the Key? An Investigation Into the Metabolic Effect of Diet

By Ellen Feldman, MD

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

SYNOPSIS: Researchers found that among adults seeking to maintain weight loss, consumption of a low-carbohydrate diet led to the highest total energy expenditure.

SOURCE: Ebbeling CB, Feldman HA, Klein GL, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: Randomized trial. *BMJ* 2018; Nov. 14;363:k4583.

Even today in our highly specialized, technologically advanced world of medicine, the centrality of diet to health is undisputed. However, what does remain in dispute are the specifics about dietary recommendations. Models and theories promoting a variety of dietary measures for disease treatment and control are numerous, and all too often studies have conflicting results.[1] The lay

Summary Points

- The authors of this randomized trial investigated the effect of varying dietary carbohydrate levels on total energy expenditure during weight maintenance.
- Weight maintenance occurs when total energy expenditure — the cumulative effect of basal metabolic rate, thermic effect of food, and activity level — is balanced with total energy from food ingested.
- After achieving weight loss, 162 eligible adults were randomized to specified carbohydrate level diet — high (60%), medium (40%), or low (20%).
- All diets were controlled for protein and adjusted to maintain weight over 20 weeks.
- Total energy expenditure, measured by doubly labeled water analysis, varied by diet, with 209 kcal/day more expenditure in the low- compared to the high-carbohydrate group and with a more pronounced 278 kcal/day greater expenditure in these same groups when considering only the subgroup completing the protocol.

press has published numerous articles proclaiming health benefits and successful weight control from diets as varied as the ketogenic diet, Whole30, and intermittent fasting. Yet, scientific data supporting such claims are lacking, and there are growing concerns about health problems, such as micronutrient deficiencies and cardiovascular safety problems, with long-term use of such diets.[2,3]

To bring some clarity to the field, Ebbeling et al conducted a randomized study with a narrow focus on energy expenditure varying with diet during maintenance of weight loss. The group did not look at the weight loss phase, did not use weight as an outcome measure, and did not look at any health outcomes beyond the 20-week study period. The primary outcome was a measure of energy expenditure. Secondary outcomes were differences in physical activity and metabolic hormones. All patients effectively completing the study maintained weight via a process of diet adjustment. Ebbeling et al stated that their work contributes to the understanding of metabolic variations induced by diet, and could lead to recommendations essential in the treatment of obesity.

An understanding of the carbohydrate-insulin model of obesity is useful to put this study in perspective. Basically, this model looks at insulin levels following ingestion of high carbohydrate load. The model suggests that higher ratios of insulin to glucagon lead to greater storage of fuel in fat tissue and that this state increases hunger and cravings for food and lowers energy expenditure, especially in persons with constitutionally high insulin secretion. However, controlled studies have not supported this model.[4]

Energy expenditure refers to the overall effect of energy required for basal metabolism (metabolic functions while at rest) plus the energy needed to absorb and digest food (thermic effect) plus energy required for activity. In simple terms, weight gain occurs when energy from food is greater than the total energy expenditure. For weight maintenance, balance among these components is necessary.[5]

This study began with a 10-week "run-in phase" during which time participants were monitored closely, provided with meals, and given an activity level to promote weight loss of 10-14%. All participants were between the ages of 18 and 64 years and had a starting body mass index > 25 kg/m^2. Participants were recruited from several college campuses and were given stipends for participation. Those who achieved the targeted weight loss were eligible for participation in the randomized potion of the study.

The researchers randomized 162 participants to either a high-, medium-, or low-carbohydrate diet for 20 weeks. For all three diets, the protein level was fixed at 20% of total energy. Carbohydrate and fat content varied inversely; the high-carbohydrate diet contained 60% of energy from carbohydrates and 20% from fat; the moderate-carbohydrate diet contained 40% of energy from carbohydrates and 40% from fat; and the low-carbohydrate diet contained 20% of energy from carbohydrates and 60% from fat.

Energy expenditure (the sum of basal metabolic rate, activity level, and thermic effect of food) was calculated via analysis of urine samples after administration of doubly labeled water. This technique for measuring energy expenditure has been used to measure energy expenditure in humans since the 1980s. The process involves substituting an isotope for oxygen and hydrogen in water molecules, and then examining urine samples to determine average metabolic rates.[6]

Table 1: Energy Expenditure and Secondary Outcomes by Diet				
	High-carb diet (60% carb)	**Medium-carb diet (40% carb)**	**Low-carb diet (20% carb)**	***P* value between groups**
Total energy expenditure (kcal/day) Intention-to-treat (n = 162) Mean change (95% CI)	-19 (-104 to 66)	71 (-12 to 155)	**190 (109 to 270)**	**0.002**
Total energy expenditure (kcal/day) Per-protocol (n = 120) Mean change (95% CI)	-102 (-201 to -2)	29 (-64 to 123)	**176 (87 to 265)**	**< 0.001**
Total physical activity (counts/d) Intention-to- treat (n = 162) Mean change (95% CI)	-26.3 (-52 to -0.6)	-42. 4 (-67.7 to -17.1)	-6.9 (-31 to 17.1)	0.13
Total physical activity (counts/d) Per-protocol (n = 120) Mean change (95% CI)	-29.1 (-59 to 0.7)	-48.3(-76.3 to 20.3)	-11.6 (-38.2 to 14.9)	0.17
Ghrelin (pg/mL) Intention-to-treat (n = 162) Mean change (95% CI)	-4.9 (-8.4 to -1.2)	-8.7 (-12 to -5.3)	**-11.8 (-14.8 to -8.6)**	**0.02**
Ghrelin (pg/mL) Per-protocol (n = 120) Mean change (95% CI)	-5.9 (-10.1 to 1.5)	-8.0 (-11.8 to -4.0)	**-13.5 (-16.9 to -10.0)**	**0.02**
Negative energy expenditure implies sum of basal metabolic energy expenditure, thermic effect of food, and activity level is less than energy derived from food intake. Bold = statistically significant				

Ebbeling et al reported two sets of data: intention-to-treat group (all participants post "run-in phase"; n = 162) and per-protocol group (data only from the participants who maintained weight during the 20-week test phase and completed all study requirements; n = 120). Table 1 shows energy expenditure measured by doubly labeled water for each specified carbohydrate diet level (high, medium, or low) in the intention-to-treat group and the per protocol subgroup.

Secondary outcome measures included time spent in physical activity. There was no significant difference among the groups in this area, nor was there a difference in time spent in sedentary activities. Ghrelin, known as the "hunger hormone," was significantly lower among those in the low carbohydrate diet.

To determine if high insulin secretors were more vulnerable to changes in energy expenditure linked to variations in carbohydrate load, each participant was assessed at baseline for fasting glucose and serum level of insulin secretion after oral glucose administration. Three groups were determined (high, medium, and low insulin secretors) based on response. Table 2 shows each of these three insulin secretor groups and compares energy expenditure in each across high- to low-carbohydrate diets (includes the intention-to-treat and per-protocol groups).

■ COMMENTARY

The popular press seemed to embrace this study. The "Today" Show proclaimed: "For weight loss maintenance, a low-carb diet may be best."[7] CNN and other media outlets followed with similar themes.[8,9] However, behind the headlines, significant questions from the scientific community remain regarding methodology and applicability to the general population. To be fair, Ebbeling et al explicitly noted in their conclusion that additional research is necessary to confirm conclusions and generate recommendations for the

Table 2: Change in Total Energy Expenditure		
	Change in total energy expenditure low- to high-carb diet: Intention-to-treat (n = 162)	**Change in total energy expenditure low- to high-carb diet: Per protocol (n =120)**
Lowest 1/3 insulin secretors	132 kcal/day $P = 0.19$	135 kcal/day $P = 0.21$
Middle 1/3 insulin secretors	164 kcal/day $P = 0.13$	246 kcal /day $P = 0.04$
Highest 1/3 insulin secretors	308 kcal/day $P = 0.004$	478 kcal/day $P < 0.001$
Comparing low- vs. high-carbohydrate diet in each of three groups representing levels of insulin secretion (determined at baseline by measuring insulin level after glucose challenge).		

public. Perhaps the most consistent criticism in the literature regarding the study is the use of doubly labeled water as the measure of energy expenditure. It is thought that the changes noted in measurements of energy expenditure may reflect an artifact of methodology due to differences in fat oxidation under conditions of high-fat and low-carbohydrate diets.[10] Although Ebbeling et al did not agree with this particular point, they noted that relying on this method to measure energy expenditure has definite limitations and requires assumptions that may not be completely accurate.

Notably, relying on any measures of energy expenditure rather than actual weight change makes it difficult to translate the results into usable recommendations for patients or the public. In the study, efforts were made to maintain weight loss throughout the 20-week test phase. These efforts are described as "adjustment of energy intake to achieve weight stability." However, if the low-carbohydrate diet had the highest rate of energy expenditure, it may be expected that this group would either lose weight during the 20 weeks or ingest more calories to prevent weight loss. As there was not a significant difference in weight change among any of the groups at the conclusion of the study, it would be useful to know if, in fact, the low-carbohydrate group consumed more calories. This may be an avenue for future investigation and would be helpful to translate the findings to usable recommendations.

Ebbeling et al noted there were significant efforts to ensure dietary compliance throughout the study, including supplying all participants with prepared meals and WiFi scales and performing spot checks for diet and weight compliance. However, even with these efforts, compliance and weight accuracy cannot be guaranteed; future investigators may be able to implement newer technologies to determine accuracy and compliance.

On a related note, a major barrier to applying findings from this study to the general population is the need to obtain dietary compliance. Following a strict low-carbohydrate diet could be challenging for many in the obese population. Additionally, since the low-carbohydrate diet included a high percentage of calories from fat (60%), from a health prospective it is imperative to make certain that following such a diet does not introduce unintended health risks.

Finally, as with many preliminary studies, several unknown or unmeasured factors need identification over time. As previously alluded, the diets differed in both fat and carbohydrate levels. Although the proportion of saturated to unsaturated fat was consistent in all groups, the actual amount of fat varied. Because of the need to change levels of macronutrients, the foods in the diets were different. Both factors — varying amounts of fat and food differences — may have introduced variables that affected the study results.

The take-home message from this study is that there is suggestive evidence that diet can influence metabolism, and that a low-carbohydrate diet may be best for increasing metabolic energy, especially in high insulin secretors. There is no evidence at this point that these findings translate seamlessly to dietary recommendations for weight loss, but suggestive evidence for patients wanting weight-loss maintenance.

Finally, it is reasonable to remember that an effective diet depends on patient acceptance, understanding, and willingness to implement. Dietary compliance is a multifactorial process determined on many levels with not only medical influences, but also societal, cultural, and economic influences. Developing an understanding of these and other factors with each patient will allow clinicians to create an individualized diet as part of a holistic treatment plan. ■

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BONE HEALTH

ABSTRACT & COMMENTARY

The Effect of Vitamin D Supplementation on Fractures, Falls, and Bone Mineral Density

By Jessica Orner, MD

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

SYNOPSIS: The authors of this systemic review, random-effect meta-analysis, and trial sequence analysis suggested that vitamin D supplementation does not have clinically significant effects on bone mineral density or the prevention of fractures or falls.

SOURCE: Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: A systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol* 2018;6:847-858.

Evidence from the early 2000s seemed to suggest benefit to musculoskeletal health from vitamin D supplementation.[1] However, more recent studies refute this claim. Authors of a Cochrane Review published in 2014 found that taking only vitamin D was unlikely to prevent osteoporotic fractures in older adults.[2] However, vitamin D supplementation combined with calcium seemed to slightly reduce the likelihood of fractures.[2]

Of late, data suggest that vitamin D supplementation may not prevent fractures or falls. Furthermore, supplementation may not have any clinically significant effect on bone mineral density (BMD). Bolland et al conducted a systematic review, random-effects meta-analysis, and trial sequential analysis to ascertain the effects of vitamin D supplementation on fractures, falls, and bone density.[3] Funded by the Health Research Council of New Zealand, the study included 81 randomized, controlled trials that reported fractures, falls, or BMD.

Summary Points

- Vitamin D supplementation does not have clinically meaningful effects on bone mineral density nor prevention of fractures or falls.
- Using a threshold of 15%, 10%, or 7.5% relative risk reduction in falls or fractures, further similar trials are unlikely to alter this study's conclusion.
- The effect of vitamin D doses ≥ 800 IU appears similar to doses < 800 IU/day.

This authors did not focus on coadministration of calcium and vitamin D supplements, since no large trials analyzing falls or fractures have become available since the previous systematic reviews of 2014. Nor did they evaluate dietary intake of calcium.

The researchers began by using their literature searches from previous meta-analyses published in 2014-2015. Subsequently, they searched PubMed in December 2015 for randomized, controlled trials and systematic reviews of vitamin D in adults. From these searches, they identified studies with outcomes of fractures, falls, or BMD. Finally, in September 2017 and February 2018, they conducted a search of "vitamin D" and other key words using PubMed, Embase, Cochrane Central, and two clinical trial databases.

Inclusion criteria were randomized, controlled trials in adults > 18 years of age; trials comparing vitamin D supplements with untreated controls, placebo, or lower-dose vitamin D supplements (i.e., doses < 800 IU per day); multiple intervention trials if the study groups differed only by the use of vitamin D; and quasi-randomized and open-label trials. Exclusion criteria were trials of hydroxylated vitamin D analogues, such as paricalcitol or doxercalciferol, and trials reporting BMD using techniques other than dual-energy X-ray absorptiometry.

They included randomized, controlled trials for specific disease or conditions likely to affect bone turnover but initially analyzed the data separately. If analysis results were similar, the trials were pooled in subsequent analyses. For trials comparing different dosages of vitamin D supplementation, high-dose vitamin D supplementation was considered ≥ 800 IU/day and low-dose was < 800 IU/day.

Primary endpoints were at least one fracture or fall. Secondary endpoints were the percentage change in BMD from baseline of the total body, total hip, femoral neck, forearm, and lumbar spine.

Trial sequence analysis (TSA) was completed for each outcome. Although TSA has been in use for more than 40 years, software that can perform TSA more easily is available free of charge through the Copenhagen Trial Unit, allowing more researchers to use this type of analysis.[4] This cumulative meta-analysis reduces the risk of false-positive results by estimating the optimum sample size for statistical inference, thresholds for statistical significance, and thresholds for futility. This type of evaluation is useful when the number of participants in a meta-analysis may be insufficient because using a 95% confidence interval can lead to false-positive conclusions. Bolland et al noted this is the first TSA of vitamin D supplementation and BMD.

Researchers also assessed the futility boundary for the primary and secondary outcomes. Futility boundaries identify settings in which it is fruitless to continue a clinical trial or study. One example is if no useful information will be obtained by adding similar studies to a meta-analysis.[5]

For falls and fractures, the initial relative risk reduction threshold was 15%. Increasingly smaller thresholds were used until the optimal sample size exceeded the actual sample size. For BMD, the threshold for BMD increase initially was set at 3%, and then researchers evaluated progressively smaller thresholds.

When available, researchers also assessed the 25-hydroxyvitamin D (25(OH)D) levels reported in the studies. Of the 81 trials, 72 were completed in populations with a mean baseline 25(OH)D concentration < 50 nmol/L (20 ng/mL), while concentrations were < 25 nmol/L (10 mg/mL) in four trials. Moreover, 76 trials reported achieving a 25(OH)D concentration of ≥ 50 nmol/L. Populations in 44 studies achieved a concentration of 75 nmol/L (30 ng/mL).

In the majority of randomized, controlled trials, researchers studied vitamin D supplementation as monotherapy in populations of community-dwelling women. The preponderance of participants were 65 years of age or older. The average dose of vitamin D was > 800 IU/daily for a duration of less than one year.

An analysis of 36 trials showed that vitamin D supplementation had no effect on total fracture (n = 44,790; relative risk [RR], 1.00; 95% confidence interval [CI], 0.93-1.07). Also, supplementation had no effect on hip fracture (20 trials; n = 36,655; RR, 1.11; 95% CI, 0.97-1.26). Regarding falls, an analysis of 37 trials showed no significant effect from supplementation (n = 34,144; RR, 0.97; 95% CI, 0.93-1.02).

Bolland et al reported there was no consistent increase in BMD over the trial duration. Also, the difference in BMD between study groups (vitamin D vs. control, high-dose vs. low-dose vitamin D) at the trial endpoints was low. Specifically, the differences were: 0.13% for total body (-0.16 to 0.42), 0.34% (0.13-0.55) for total hip, 1.12% (0.58-1.65) for femoral neck, 0.25% (0.00-0.49) for lumbar spine, and -0.16% (-0.46 to 0.13) for forearm. Notably, one study that had a between-group difference of 10.6% later was excluded from analyses because it was determined to be an outlier. This led to the femoral

neck difference changing to 1.12% (0.58-1.65). For the primary endpoints in this study, the estimated effect size lay within the futility boundary for RRs of 15%, 10%, and 7.5%, offering support to the determination that vitamin D supplementation does not reduce fractures or falls. Further similar studies are unlikely to change this conclusion. For BMD, the estimates for total body, total hip, and forearm were within the futility boundary for a between-group difference of 0.5%. For the lumbar spine and femoral neck, a between-group difference of 1.0% was within the futility boundary.

■ COMMENTARY

The most interesting part of this study was the use of TSA to determine if the addition of future studies would change the outcome. It appears that for the primary and secondary endpoints, future studies would not make a significant difference. However, there is room for further evaluation of supplementation at lower 25(OH)D concentrations, as well as combination therapy with calcium or magnesium.

Only four trials included reported baseline 25(OH)D concentrations < 25 nmol/L (10 mg/mL). In a recent study published in the *Journal of Bone and Mineral Research*, researchers reported significant treatment effects at the spine and hip with vitamin D 1,000 IU/day over a year in participants with a baseline 25(OH)D ≤ 30 nmol/L (12 ng/mL).[6] In a study of 344 middle-aged women, researchers suggested 25(OH)D levels of 29-33 nmol/L are required for optimal musculoskeletal health.[7] It would be beneficial to conduct a large meta-analysis and TSA that included more studies with baseline 25(OH)D of ≤ 30 nmol/L to determine if this population may benefit from supplementation.

It also is important to note that although the researchers did not find increased BMD differences over the trial duration between trial groups, the pooled analysis using the final trial timepoints showed differences between the trial groups. Whether these differences were present at the onset of the trials was not discussed. This appears to be a flaw in their study and report. More commentary from the researchers would be helpful.

The meta-analysis included quasi-randomized trials, which can lead to greater risk of selection bias because participant allocation to different trial arms may not truly be random and may be based on factors such as order of recruitment or medical record number.

There was no comment on the quality of the vitamin D supplements. However, it is not clear that using high-quality supplements would change the outcomes. Correspondingly, it would be thought-provoking to see research on the comparison of vitamin D supplementation vs. dietary sources of vitamin D with and/or without calcium.

Based on this trial, vitamin D supplementation would not be useful for reducing falls or fractures in those with 25(OH)D levels > 30 nmol/L. More commentary from the researchers is needed to clarify the usefulness of vitamin D supplementation on BMD. Providers should check vitamin D levels prior to starting patients on vitamin D supplementation if considering it as a preventive therapy for falls or fractures. ■

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AGING

SHORT REPORT

Exercise and the Aging Immune System

By David Kiefer, MD, Editor

SYNOPSIS: The authors of this literature review detailed changes in immune system function that occur with age, as well as the immunological effects of acute and chronic exercise.

SOURCE: Sellami M, Gasmi M, Denham J, et al. Effects of acute and chronic exercise on immunological parameters in the elderly aged: Can physical activity counteract the effects of aging? *Front Immunol* 2018;9:2187.

The ambitious title of this review certainly elevates our hopes in the quest to reverse, or at least stave off, the effects of aging. Although not a structured meta-analysis, the authors collected and cited studies across the spectrum of physiology to controlled clinical studies to make an argument for the benefits of exercise on immune system function, focusing on the elderly population. They focused on individuals aged 65 years and older, although they had to extrapolate, at times, from research on younger individuals when studies were lacking. They began their review by detailing the changes in the immune system that occur with age; they used the terms "immunosenescence" and "immunopause." See Table 1 for some of the changes.

In general terms, the authors mentioned that various types of exercise, at least partly, can ameliorate these immune system changes and inflammation, and even bolster the effect of the flu vaccine, although these effects depend on the type of exercise (e.g., acute vs. chronic; form: endurance, resistance, or sprint; duration; intensity; etc.). Some of these changes are mediated by catecholamines, growth hormone, and glutamine. The researchers also noted that there might be a gender effect on some of the results (i.e., effects seen in men but not women, or vice versa). There also may be effects seen in the elderly that would be different in younger populations, although most of the research has been done on the latter demographic. They expanded on this by splitting the research findings into "acute" and "chronic" exercise; acute exercise involved a single exercise event, whereas chronic exercise was subdivided further into endurance, resistance, and sprint activities. For acute exercise, increased blood flow and other changes may rally immune system cells and stimulate the bone marrow, leading to various improved immunological parameters. (*See Table 2.*) Most immune system cell lines are affected by acute exercise. Of note, the authors found little to no convincing evidence on changes to cytokines and interleukins.

Table 1: Changes in the Immune System and Cytokines That Can Occur With Increasing Age

- Thymus atrophy
- Decrease in lymphopoiesis (more myeloid cells)
- Decrease in antibody production
- Fewer naïve T cells
- Fewer hematopoietic stem cells
- Increased secretion of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-alpha)

Summary Point

- All types of exercise have positive effects on the immune system, helping to correct the changes seen with "immunopause"; the only exceptions would be some short-term detrimental effects to exercise that qualifies as high-intensity.

With respect to "chronic" exercise (*see Table 3*), the first category is endurance training, or low-to-moderate effort exercise. With endurance training, there is a general improvement in immune system function, except with long-term intense exercise, which can adversely affect the immune system and lead to an increase in risk for

Table 2: Immune System Changes Shown to Occur After 'Acute' or Single Exercise Events
• Increase in number of monocytes • Increased neutrophil number • Increased number of circulating neutrophils • Longer telomere length in leukocytes (with moderate exercise) • Increased number of circulating lymphocytes • Leukocytosis (neutrophilia, lymphocytosis) • Increased natural killer cell number and function

Table 3: Effects of 'Chronic' Exercise, Such as With Endurance, Resistance, and Sprint Training Regimens
• Tai chi increases circulating myeloid dendritic cells • Endurance training increases numbers of stem cells • Increased neutrophil phagocytic activity with resistance training • Increased cytokines with sprint training • Decreased neutrophil function with sprint training

infections. The next category is resistance training, which involves the voluntary use of skeletal muscles. The researchers mention "ambiguity" in the literature, both with conflicting results or no effects, although there may be some changes in neutrophil activity. (*See Table 3.*) Finally, sprint training usually involves short periods of running exercise, and has a mixed effect on immune parameters, such as decreasing neutrophil function but increasing cytokines.

In previous issues of *Integrative Medicine Alert,* we have reviewed numerous articles touting the benefits of exercise for various demographics. Add to it the results nicely summarized by Sellami et al of exercise, both in general and in the elderly. The effects are complicated and mitigated by many factors, most importantly the type and duration of exercise. And there is a lack of research in the elderly, especially for some exercise types (especially sprint training) and immune parameters (little research on basophils and eosinophils, for instance). Clearly, more data are needed.

Overall, it seems that all types of exercise have some positive effects on immune system function, helping individuals address "immunopause." However, there are important caveats, such as the fact that intense endurance training or sprint training may compromise immune system function depending on the exact type of exercise. Keeping in mind these risks, this review reaffirms that clinicians can confidently weave in activity recommendations for their elderly patients, individualized based on mobility issues and comorbidities. Both acute and chronic exercise regimens can bolster the immune system in physiologically important ways. ■

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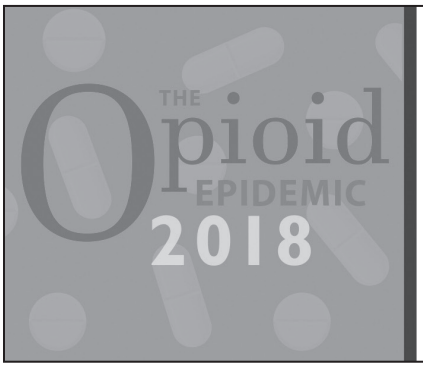

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CME QUESTIONS

1. According to the study by Pour et al, which of the following is true regarding the use of lettuce to treat sleep in pregnant women?

a. Capsules of the seed were used.
b. The species studied was wild lettuce (*Lactuca virosa*).
c. In the treatment group after two weeks, there was an increase in the PSQI score.
d. Women suffered from significant gastrointestinal upset, different than the placebo group.

2. Which of the following statements is true based on results of the article regarding carbohydrate levels and energy expenditure?

a. This was a prospective, randomized study of metabolic measures of energy expenditure during weight-loss maintenance. The authors found evidence of increased energy expenditure with low-carbohydrate diets.
b. This was a retrospective study of metabolic measures of energy expenditure during weight-loss maintenance. The authors found evidence of weight loss with a low-carbohydrate diet and lower energy expenditure with a higher-carbohydrate diet.
c. This was an observational study during weight loss maintenance. The authors found increased activity, increased energy, and decreased consumption of calories in those following a low-carbohydrate diet.
d. This was an observational study during weight loss and maintenance phases. The authors found significant increases in energy expenditure with a low-carbohydrate diet but no change in overall weight.

3. What endpoints were assessed in the trial on vitamin D supplementation and musculoskeletal health?

a. Falls, bone mineral density, and functioning
b. Functioning, falls, cognitive improvement
c. Bone mineral density, falls, and fractures
d. Fractures, functioning, cognitive improvement

4. Which of the following immune system changes can occur with "chronic," or long-term, exercise regimens?

a. A decreased number of stem cells from endurance training
b. Increased circulating myeloid dendritic cells from tai chi
c. Decreased cytokines from sprint training
d. Decreased neutrophil phagocytic activity from resistance training

CME OBJECTIVES

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.

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