AHC Media

Integrative Medicine

Vol. 18, Issue 1, January 2015
www.ahcmedia.com

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

AGING

ABSTRACT & COMMENTARY

Run, Don't Walk: Benefits for Older Adults

By David Kiefer, MD

SYNOPSIS: This study compared the metabolic cost for walking three different speeds in 30 adults at least 65 years of age, and found that those who ran on a regular basis expended less energy walking than the group that walked exclusively.

SOURCE: Ortega JD, et al. Running for exercise mitigates age-related deterioration of walking economy. *PLoS One* 2014;9:e113471.

What is the key to staving off the effects of aging and promoting healthy longevity in all of its parameters? There are many facets to this question, one of which pertains to physical morbidity. This article compared walking to running and their effects on "metabolic cost" (explained below), and the result was compelling enough that even the editors of the *New York Times* featured it in a recent article.

As people age, it becomes more difficult to do physical tasks, including the simple act of walking, and this deterioration correlates with a myriad of health outcomes. One way to measure this difficulty with physical activity, specifically pertaining to walking, is to calculate the metabolic cost for walking, also called the "economy" of walking. Prior studies have found a worsening economy with walking as people age. The authors of this study cite prior research showing a decreased muscular efficiency — perhaps even a greater firing of antagonistic muscles — with walking that may be related to this decline in walking economy. It isn't too difficult to imagine, then, the connection with activities of daily living such as balance, transfers, and fall risk. Prior studies also show, again as cited by the authors, that older runners have a similar running economy to younger runners, but it is unknown how older runners compare to older walkers when it comes to *walking*. This, then, speaks to the utility of intensive training regimens to mitigate the decline in walking economy. This trial was designed to shed some light on the physiology of walkers vs runners when it comes to economy of walking.

Thirty volunteers were solicited (*see Table 1*), all of

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Leslie Hamlin report no financial relationships relevant to this field of study.

Integrative Medicine [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Integrative Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com
www.ahcmedia.com

Questions & Comments:
Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits™*: $319
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $269

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of ***24*** *AMA PRA Category 1 Credits™*. Each issue has been designated for a maximum of 2.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 24 AOA Category 2-B credits.

This CME activity is intended for physicians and researchers interested in integrative medicine. It is in effect for 36 months from the date of the publication.

AHC Media

Table 1: Study Participants: Running vs Walking and Gender Breakdown

	Men	Women
Runners	10	5
Walkers	4	11

whom were 65 years of age or older, in line with a median age when a decline in walking economy often occurs. All participants either walked or ran 30 minutes at least three times per week, for at least 6 months before the inception of the study. Study participants attended three sessions, as detailed in Table 2. In short, the metabolic rate for each study participant was measured at rest as well as three walking speeds on a treadmill. The three speeds were 0.75, 1.25, and 1.75 meters per second. As a reference, the middle speed corresponds to 2.8 miles per hour, a relatively brisk walking speed. The metabolic rate was calculated by measuring the rates of oxygen (VO_2) and carbon dioxide (VCO_2) consumption. Further calculations included ground reaction forces (from settings on the treadmill), metabolic power consumption (from oxygen and carbon dioxide usage, and body weight), and gross metabolic cost of transport (metabolic power consumption divided by speed).

The researchers found runner vs walker differences. For example, gross metabolic cost of transport was 7-10% less in runners across all walking speeds (P = 0.016), even though the standing, resting metabolic rates were similar. Statistics showed that this difference was not due to gender, nor stride variables and kinetics such as stride time and swing time. However, the stride length in runners was 6% less than in walkers (P = 0.33).

The researchers then tapped into a database of similar data encompassing people of different ages, and compared the gross metabolic cost of transport, again the gross metabolic power as a function of speed. They found that older walkers consumed energy at a rate similar to older sedentary adults (P = 0.46), older walkers consumed energy 14.22% faster than young sedentary adults (P < 0.001), older runners consumed energy slower (percentage not supplied) than older sedentary adults (P = 0.016), and older runners consumed energy similar to young sedentary adults (P = 0.237). The authors postulate that these findings show that older walkers are unable to stop the deterioration in metabolic cost of walking because they have the same gross metabolic cost of transport as older sedentary adults.

■ COMMENTARY

We are all aware of the epidemic of sedentary lifestyles in the United States and the guidelines that exist to change that. Clinicians have tried the "exercise prescription" and attempted to nudge patients toward the 150 minutes per week of moderate-intensity exercise oft recommended.[1] But, is all exercise the same for all people? And, what about for older adults who are particularly at risk for the adverse effects of waning strength and mobility? Some recommendations tailor exercise suggestions for specific demographics, such as for those people trying to lose weight.[2] There may also be benefits to more vigorous activity when it comes to overall health and longevity.[3]

This trial, although small and with important gender differences between the two groups, seems to provide some support that there are benefits to a regular running practice in older adults. Adults older than age 65 years who ran at least

Table 2: Details about the Three Sessions Attended by Study Participants

Session 1	Session 2 (5 days after 1)	Session 3 (2 days after 2)
• Physical exam • Body composition exam to determine body fat • VO_2 treadmill test to determine maximum aerobic capacity	• Standing metabolic rate • Practiced on treadmill: three speeds, 7 minutes each speed	• Measured quiet standing metabolic rate • Measured metabolic rate at the three speeds for 5 minutes each

Summary Points

- Older runners have 7-10% less metabolic cost for walking than older walkers.
- It is possible that running increases muscle strength and reduces antagonistic muscle activation, accounting for some of this decreased metabolic cost.
- These results have implications for exercise training, and forestalling the morbidity that occurs with impaired walking performance.

30 minutes three days a week had less metabolic cost for walking than their walking counterparts. This improved metabolic efficiency protected them from the age-related decline in "walking economy," keeping the runners like young (sedentary) adults, whereas older walkers followed the same downward trend in efficiency as older sedentary adults. The authors tie this research into work showing that intense training in older adults can increase muscular efficiency and stop antagonistic muscle firing, two of the mechanisms that are thought to be related to making runners less metabolic cost for walking. So, it seems, this study showed some quantifiable clinical effects, and there was a plausible mechanism, perhaps enough for clinicians to raise their eyebrows and give this serious consideration.

Of course, as the authors mentioned, this trial should be expanded in size, and its methodology improved (beyond simply a cross-sectional analysis) to definitively change the way we approach exercise recommendations in this demographic. Until then, it is a reminder to continually address this aspect of whole person care; to reiterate the importance of some form of activity for all patients; and to explore that an increased intensity, when it can be safely done, may have some benefits for older adults above and beyond walking. ■

REFERENCES

1. Office of Disease Prevention and Health Promotion. Physical Activity Guidelines. Available at: www.health.gov/paguidelines. Accessed Dec. 16, 2014.
2. Centers for Disease Control and Prevention. Healthy weight — it's not a diet, it's a lifestyle. Available at: www.cdc.gov/healthyweight/physical_activity/index.html?s_cid=govD_dnpao_006. Accessed December 18, 2014.
3. Wen CP, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *Lancet* 2011;378:1244-1253.

DIETARY SUPPLEMENTS

ABSTRACT & COMMENTARY

Vitamin D Supplementation: What's the Verdict?

By Luke Fortney, MD

Wellness Programs Medical Director, Meriter Medical Group, Madison, WI

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

SYNOPSIS: Large-scale observation data indicate an inverse association with circulating vitamin D levels and risk of death due to all causes, particularly cardiovascular and cancer-related death, while supplementation with vitamin D3 appears to reduce overall mortality among older adults.

SOURCE: Chowdhury R, et al. Vitamin D and risk of cause specific death: Systemic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;348:g1903. doi: 10.1136/bmj.g1903.

For the past 20 years, vitamin D has slowly and steadily gained interest among the lay public and researchers alike. Unlike the popular histories of other vitamin supplements,[1] vitamin D has shown consistent and growing promise as an efficacious health intervention for reduction of cardiovascular and cancer-related death. More recently, this large systemic review and meta-analysis of 73 observational cohort studies involving nearly 900,000 participants, and of 22 randomized controlled trials (RCT) including more than 30,000 participants, supports the argument that that vitamin D is important for health and prevention. The authors of this review conclude that there is an inverse association of 25-hydroxyvitamin D serum levels with risks of death due to cardiovascular disease, cancer, and other causes. Similarly, supplementation

Summary Points

- There appears to be a significant deleterious role of low vitamin D levels in all-cause mortality, while supplementation with vitamin D3 appears to be superior to D2 in prevention of all-cause mortality among older adults.
- Overall evidence from almost 900,000 participants in 26 different countries reveals an inverse association of circulating vitamin D levels with risk of all-cause mortality, particularly death from cardiovascular disease and cancer.
- Supplementation with vitamin D3 vs D2 appears to significantly reduce overall mortality among older adults.
- Despite associations with vitamin D and mortality outcomes, highly convincing evidence for widespread vitamin D supplementation is currently lacking and further research is still needed.

with vitamin D3 also appears to reduce overall mortality among the elderly. What remains unknown is whether supplementation of vitamin D2 vs D3, in what groups of people, at what stage of the lifecycle, for how long, and at what optimal dose, may most favorably effect morbidity and mortality outcomes.

■ COMMENTARY

This large review and meta-analysis contributes further evidence in favor of addressing vitamin D deficiency (< 20 ng/mL) and insufficiency (20-30 ng/mL) among most adults. In looking at 73 cohort studies comparing low and normal vitamin D serum levels, as well as 22 randomized, controlled trials where vitamin D was given alone vs placebo, the authors of this large and thorough review report encouraging findings that suggest moderate but significantly meaningful risk reduction for all-cause mortality that may actually be on par with other health risks such as smoking, alcohol consumption, and physical inactivity.

Stepping back to look at the history of vitamin D begins in the 19th century when vitamin D deficiency was identified as a cause of rickets, particularly in children living in industrialized urban areas. This observation lead to a responsive public health movement that began supplementing various foods with vitamin D, which in turn resulted in decreased health problems from vitamin D deficiency. More recently, however, low vitamin D has been linked with other conditions among people of all ages, but especially the elderly, poor, and chronically ill. However, more current research continues to show that many young healthy individuals without any identifiable risk factors were still found to have very low levels of circulating vitamin D.[2]

The physiology and pathogenesis of vitamin D metabolism and deficiency is complex and involves multiple steps worth reviewing briefly (*see Figure*). Activation begins with ingestion of either ergocalciferol (D2 extracted from irradiated yeast and plant sterols) or cholecalciferol (D3 obtained from oily fish), or by UVB irradiation of 7-dehydrocholesterol in the skin. These precursors then circulate to the liver, where they are hydroxylated into 25-hydroxyvitamin D (the preferred clinical laboratory test for vitamin D). From there, 25-hydroxyvitamin D circulates to the kidneys, where it is further hydroxylated into 1,25 dihydroxyvitamin D, which is the most metabolically active form in the body.

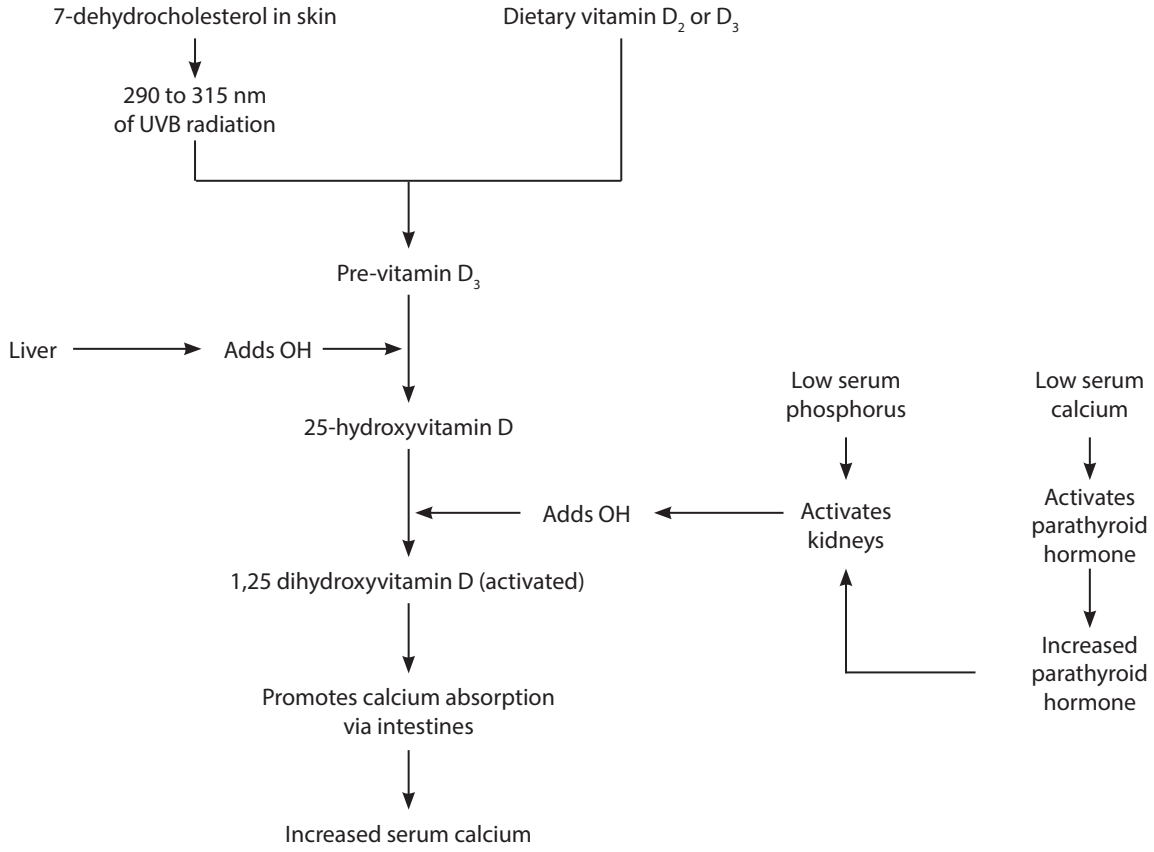
Feedback loops involving absorption of calcium in the intestines and calcium detection by the parathyroid glands also play a key role in activating, mobilizing, and maintaining vitamin D levels, which is important for a host of biological processes such as cellular growth and regulation among many others. What's more, there are approximately 3000 different binding sites for vitamin D throughout the human genome, and receptors are present in all human tissues, indicating a wide range of known and yet unknown functions.[3] Risk factors for vitamin D deficiency include age > 65 years, breastfeeding mothers, darkly pigmented skin, insufficient sunlight exposure, certain medications (e.g., antipsychotics, anticonvulsants, and glucocorticosteroids), obesity, physical inactivity, liver and kidney disease, other chronic illnesses, and low socioeconomic status.[4]

What has been less clear in the past 10 years is what role vitamin D plays in various other conditions such as depression, chronic pain, cancer, hypertension, diabetes, acute respiratory infections, and other infections. Other clinical questions include who should be screened for vitamin D deficiency/insufficiency, at what times of the life cycle, and how often.

Returning to the review by Chowdury et al, the strengths of this meta-analysis are numerous. First, it sheds light on some of the most important public health questions regarding vitamin D, namely: 1) are low levels associated with any significant risk of premature death; 2) does supplementing with vitamin D improve mortality in meaningful ways; and 3) what form of vitamin D (e.g., D2 or D3) is preferred?

This review is also large and broad. It included analysis of more than 900,000 participants from both an observational cohort-controlled perspective, as

Figure 1: Physiology and Pathogenesis of Vitamin D Metabolism and Deficiency



well as the gold standard of 22 RCTs that compared vitamin D supplementation alone vs placebo or no treatment while controlling for obvious confounding variables. While the downfall to many meta-analyses is determining what studies to include and exclude, this review is clear and convincing in identifying the criteria used for inclusion and quality.

To start, more than 2700 studies were identified and considered. After initial screening by two separate and independent investigators, a final consensus on only 95 of these was reached by involving a third investigator. These studies were selected based on strict inclusion criteria. Study-specific relative risks were then determined and analyzed using random effects models, and finally grouped by study and population characteristics to finalize the results. This methodological approach is very appropriate in this setting, given the variability of participants (e.g., older vs younger), sample sizes, and overall effects. For comparison with previous reviews, this meta-analysis involved 10 times as many participants and three times as many mortality outcomes.

Overall, the principle findings from this review generally concur with and advance those findings from previous research studies. Unlike preceding reviews, however, this large and rigorous analysis only included RCTs that administered vitamin D, thus controlling for effects from other supplements and vitamins. This review also used pre-selected vitamin D cutoffs before making any conclusions. In comparing the bottom one-third and top one-third of reported circulating 25-hydroxyvitamin D levels among participants, there was a relative risk (RR) of 1.35 (95% confidence interval, 1.13-1.61) for death from cardiovascular disease and 1.14 (1.01-1.29) for death due to cancer for those participants with the lowest serum levels of vitamin. Additionally, the RR for non-vascular, non-cancer death and for all-cause mortality was 1.30 (1.07-1.59) and 1.35 (1.22-1.49), respectively (P values > 0.05 for all). These findings are of particular importance given that heart disease, cancer, and stroke are the number 1, 2, and 4 causes of death, respectively, in the United States, according to the Centers for Disease Control and Prevention, accounting for more than 1.2 million deaths annually.[5] By using population prevalence estimates of vitamin D deficiency from this study, this means that 12.8% of all deaths in the United States annually can be attributed to vitamin D deficiency. In other words, each 10 ng/mL decline of serum vitamin D concentration was

associated with a 16% increased risk of all-cause mortality.

Compared with other known risk factors of chronic disease and death, the risk of death due to low circulating vitamin D levels in the United States appears to be substantial at 13% vs 20% for smoking, 11% for physical inactivity, and 9% for alcohol consumption. It should also be pointed out that: 1) most of the studies included in this review were also controlled for variable lifestyle and diverse population characteristics (e.g., low socioeconomic status, insufficient sunlight exposure, poor diet, obesity, etc.); and 2) pooled estimates remained unchanged when further stratified and adjusted for these various lifestyle factors that could have affected the results.

The authors appropriately point out that caution should nonetheless be used before drawing firm conclusions, in that most vitamin D studies have only involved older individuals with a generally higher rate of death due to comorbidities anyway, and are relatively brief in terms of intervention and observation timelines (generally 1 year or less). They also emphasize the need for future RCTs over substantially longer timeframes that involve non-institutionalized general populations of significant scale and diversity. It still remains unknown what dose, type, and duration of supplementation may be needed to better understand the broader range of associated morbidity and mortality outcomes.

Before too much excitement is elicited from the conclusions of this meta-analysis, it should be noted that another recent, very large systematic review concluded that despite the encouraging associations between vitamin D and mortality outcomes, firm universal conclusions and recommendations cannot yet be made.[6]

Finally, the question of D2 vs D3 supplementation, in terms of health benefit and disease prevention, has long been unclear and debated. While the RCT aspect of this review indicated no improved mortality among older adults when given vitamin D, further stratification of the data reveal an interesting and encouraging trend. Supplementation with D3 was found to significantly reduce all-cause mortality by 11% (CI, 0.80-0.99, $P < 0.05$) compared to no overall mortality effect or protection from D2. This finding may be explained in part due to the fact that D2 is less potent and biologically active than D3.[7] Another possible explanation is the observation that, in the absence of concomitant use of calcium supplementation with D2, there is an accompanying lower 25-hydroxyvitamin D concentration compared to D3.[8]

Nonetheless, more work is needed to identify what form of vitamin D supplementation is most efficient, cost-effective, efficacious, and safe before additional widespread supplementation recommendations can be made. For the time being, the benefits appear to greatly outweigh the risks for vitamin D supplementation, when used appropriately. However, vitamin D toxicity (> 150 ng/mL) can result from taking too much vitamin D for too long (> 10,000 IU of D3 or > 50,000 IU of D2 daily for > 3 months). Taking more than 300,000 IU of vitamin D in 24 hours can also be dangerous due to significant increases in serium calcium levels. (See www.vitamindcouncil.org for more information on vitamin D toxicity)

Recent guidelines from the National Institutes of Health and the Institute of Medicine recommend supplementing with 600-800 IU of vitamin D3 daily for adults,[9] while other medical conditions (e.g., eczema and heart disease) may require 1000-2000 IU daily.[10] Recognizing that there is a dose-dependent increase of skin cancer risk with unprotected sunlight exposure, a more natural form of boosting vitamin D involves exposing the skin to sunlight (UVB) for 10-15 minutes a day for fair skinned people or up to 1-2 hours a day for very dark skinned people. More specific information on sunlight therapy for vitamin D production regarding skin types, latitude location, time of day, and time of year can be found at www.vitamindcouncil.org online. ■

REFERENCES

1. Slatore CG, et al. Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. *Am J Respir Crit Care Med* 2008;177:524-530.
2. Tangpricha V, et al. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 2002;112:659-662.
3. Ramagopalan SV, et al. A ChIP-seq defined genome-wide map of vitamin D receptor binding: Associations with disease and evolution. *Genome Res* 2010;20:1352-1360.
4. Bordelon P, et al. Recognition and management of Vitamin D deficiency. *Am Fam Physician* 2009;80:841-846.
5. Centers for Disease Control and Prevention. Leading Causes of Death. Available at: http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed Dec. 10, 2014.
6. Theodoratou E, et al. Vitamin D and multiple health outcomes: Umbrella review of systematic reviewed and meta-analyses of observational studies and randomised trials. *BMJ* 2014;348:g2035.
7. Armas LA, et al. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 2004;89:5387-5391.
8. Autier P, et al. A systematic review: Influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. *J Clin Endocrinol Metab* 2012;97:2606-2613.
9. National Institites of Health. Office of Dietary Supplements. Vitamin D. Fact Sheet for Health Professionals. Available at: http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/. Accessed Dec. 14, 2014.
10. Mayo Clinic. Vitamin D. Available at: http://www.mayoclinic.org/drugs-supplements/vitamin-d/dosing/hrb-20060400. Accessed Dec. 14, 2014.

ABSTRACT & COMMENTARY

Exercise and Gut Flora: Suggestions But No Final Answers

By Howell Sasser, PhD

Senior Lecturer, New York Medical College, Valhalla, NY

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

SYNOPSIS: Diversity of gut flora was significantly greater in highly trained athletes than in population controls, even after stratifying on the controls' body mass index. The athletes' level of exercise and diet may have been responsible, individually or jointly, for this phenomenon.

SOURCE: Clarke SF, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* 2014;63:1913-1920.

A research group in Ireland compared the nature and diversity of gut bacteria in highly trained athletes (professional rugby players) and controls chosen from the general population. All study participants were male, and most were under the age of 40. Participants gave blood and stool samples, completed a detailed food frequency questionnaire, and had several biometric measurements taken. For the presentation of results, controls were divided into two groups by body mass index (BMI) — ≤ 25 kg/m^2 and > 28 kg/m^2.

The athletes had significantly ($P < 0.009$) greater diversity of gut bacterial species as compared with the high-BMI controls. They also had significantly ($P < 0.05$ to $P < 0.009$) greater diversity as compared with the low-BMI controls on three of five indices used in the analysis. The athletes showed a significantly different mix of bacterial species as compared with both control groups, although the difference between the athletes and the high-BMI controls was more pronounced. Predictably, the athletes' diets were higher in average total energy and protein per unit of body mass than either control group ($P < 0.05$ for each comparison). Higher protein intake was significantly correlated with greater microbial diversity, irrespective of study group ($P < 0.0001$ to $P < 0.03$).

Summary Points

- Athletes had significantly greater diversity of gut microbial taxa compared with population controls.
- Athletes also reported dietary factors such as significantly higher total calorie intake and protein intake in proportion to body weight.
- These dietary factors were also associated with gut microbial diversity.

■ COMMENTARY

The results of this study are intriguing, but should be viewed as suggestive rather than conclusive for a number of reasons. First, the design of the study was cross-sectional. Information about diet, exercise, and gut flora was collected at about the same time. Also, the food frequency questionnaire with which diet details were collected covered only the most recent 30 days. This makes it difficult to infer confidently that the observed diet and exercise patterns preceded the observed variations in microbial diversity. It also is unclear what, if any, dose-response relationship there may be, or how quickly a change in diet or exercise patterns might be reflected in the gut flora.

A second issue relates to the nature of the comparisons made in the study. Those in the athlete group were professional rugby players, while those in the comparison groups were selected without respect to their usual level of exercise. A comparison of creatine kinase levels in the three groups (used as a marker of training intensity) showed that the athletes were significantly higher ($P < 0.0001$) as compared with each control group. While the results of this study may be valid, they seem unlikely to be readily adaptable to recommendations in general medical practice. Advice that a patient begin what the authors of this study themselves describe as "extreme exercise" is unlikely to be heeded.

A third issue is the lack of adjusted analyses. The

authors note that extremes of both diet and exercise may affect the composition of the gut flora. They properly collect data on both, but do not report analyses of either potential explanatory factor after controlling for the other. Since they report that the athletes' diets were different in various respects from those of the other study participants, this is an important unanswered question.

Despite these limitations, this adds to the growing evidence chain that leads from behavioral factors to the gut flora to immune function and other outcomes. There is good evidence that the gut flora are affected by diet and that this effect varies even with seasonal changes in diet.[1,2] There is less clear evidence about the role of exercise, so this paper is a welcome addition in that respect. Exercise, in moderate quantities, has long been linked with improved general health, including fewer sick days.[3] However, intense exercise has been shown to be associated with transient impairments of immune function, perhaps through the suppression of neutrophils. In turn, the role of the gut microbiota in affecting (or even "regulating") immune function has been the subject of considerable research in both animal and human models.[4,5] The present results suggest a possible line of inquiry that might clarify the role of "upstream" factors.

For the individual clinician and patient, the guidance remains largely the same. Moderate exercise most days of the week appears to produce desirable health effects with minimal risk. A dramatic increase in exercise intensity with the goal of altering immune function may or may not produce the desired result, but may also introduce new risks. The same is true of radical changes in diet. Human physiology and the bacteria in the digestive system have co-evolved and have elaborated to such an extent that short-term changes in behavior may alter their functioning, but these alterations are unlikely to be controllable, much less desirable. ■

REFERENCES

1. Scott KP, et al. The influence of diet on the gut microbiota. *Pharmacol Res* 2013;69:52-60.
2. Davenport ER, et al. Seasonal variation in human gut microbiome composition. *PLoS One* 2014;9:e90731.
3. Nieman DC, Pedersen BK. Exercise and immune function. *Sports Med* 1999;27:73-80.
4. Noverr MC, Huffnagle GB. Does the microbiota regulate immune responses outside the gut? *Trends Microbiol* 2004;12:562-568.
5. Hooper LV, et al. Interactions between the microbiota and the immune system. *Science* 2012;336:1268-1273.

HERBAL SUPPLEMENT

SHORT REPORT

Licorice as an Agent in *Helicobacter pylori* Quadruple Therapy Regime

By Carrie Decker, ND

Founder and Medical Director, Blessed Thistle, Madison, WI

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

SYNOPSIS: Individuals having peptic ulcer disease positive for *Helicobacter pylori* infection (diagnosed by endoscopy and biopsy with positive rapid urease test) were treated with either traditional quadruple therapy or quadruple therapy with licorice as a substitution for bismuth subsalicylate. After 4 weeks of treatment, eradication of *H. pylori* infection was comparable in both groups.

SOURCE: Momeni A, et al. Effect of licorice versus bismuth on eradication of *Helicobacter pylori* in patients with peptic ulcer disease. *Pharmacognosy Res* 2014;6:341-344.

Licorice, *Glycyrrhiza glabra*, has a history of traditional use for the relief of epigastric pain and as a supportive agent in the healing from peptic ulcer disease. It has known anti-inflammatory action and supports healing of the gastric mucosa. In vitro studies have demonstrated that licorice has antimicrobial effects, including bactericidal and growth inhibition against *Helicobacter pylori*.[1] There currently are multiple variations of antibacterial and acid-

Summary Point

- Licorice may support the eradication of *H. pylori* as a part of a quadruple therapy regimen including amoxicillin, metronidazole, and omeprazole.

suppressing agents used for the treatment of *H. pylori* infection, and resistance to treatments has been seen.

Sixty individuals diagnosed with peptic ulcer disease positive for *H. pylori* infection via biopsy and rapid urease test were randomized to treatment with amoxicillin (1 g twice daily), metronidazole (500 mg twice daily), omeprazole (20 mg twice daily), and bismuth subsalicylate (524 mg twice daily) or licorice (380 mg twice daily containing < 3% glycyrrhizinic acid). After 4 weeks of treatment, the success of *H. pylori* eradication was assessed by urea breath test. In the group randomized to licorice as a part of the quadruple therapy, 67% tested negative for *H. pylori* infection, while in the group randomized to bismuth subsalicylate, 57% tested negative for *H. pylori* infection. The eradication rate of *H. pylori* infection was not significantly different in either group (P = 0.428).

Although no significant adverse effects were seen, and all individuals were noted to have completed this study, non-cooperation of patients was noted as exclusion criteria for the study bringing into question the reliability of the results. In general, due to small population and treatment limited to a single proprietary licorice formulation, further studies should be performed before this information is used clinically. ■

REFERENCE

1. Krausse R, et al. In vitro anti-*Helicobacter pylori* activity of *Extractum liquiritiae*, glycyrrhizin and its metabolites. *J Antimicrob Chemother* 2004;54:243-246.

DIABETES

SHORT REPORT

Not So Sweet: Artificial Sweeteners Contribute to Dysbiosis and Glucose Intolerance

By Donald Brown, ND

Managing Director, Natural Product Research Consultants, Seattle, WA

Dr. Brown reports he is a retained consultant for Nature's Way and Linnea.

SOURCE: Suez J, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 2014;514:181-186. doi: 10.1038/nature13793. Epub 2014 Sep 17.

Researchers from the Weizmann Institute of Science in Israel demonstrated that mice consuming non-caloric artificial sweeteners (NAS; e.g., saccharin, sucralose, and aspartame) in drinking water developed marked glucose intolerance compared to mice consuming only glucose or sucrose in drinking water. A link was made to alterations in the intestinal microbiota.* To study the effect of long-term NAS consumption in humans, data were collected from 381 non-diabetic individuals (44% male and 56% females; age 43.3 ± 13.2 years) using a validated food frequency questionnaire. Significant positive correlation was found between NAS consumption and several metabolic syndrome-related parameters such as increased weight and waist-to-hip ratio (measures of central obesity), higher fasting blood glucose, glycosylated hemoglobin (HbA1c), and glucose tolerance test. HbA1c was significantly increased in a subgroup of high NAS consumers (n = 40) compared to 236 non-NAS consumers (P < 0.002), and remained significant even when the calculation was corrected for body weight (P < 0.015).

Summary Point

- Non-caloric artificial sweetener (NAS) consumption appears to increase risk of metabolic syndrome, particularly glucose intolerance.
- The findings of this study may be partially explained by a change in gut microbiota resulting in dysbiosis in persons consuming NAS.

Analysis of intestinal microbiome in 172 subjects (randomly selected from the cohort of 381 subjects) using 16S RNA gene sequencing found that suggested taxonomic changes indicative of dysbiosis.* Notably, several of the bacterial taxa that changed following

NAS consumption were previously associated with type 2 diabetes in humans.[1,2] In an assessment of seven volunteers consuming NAS (saccharin, 5 mg/kg of body weight) for 1 week, four out of seven showed impaired glucose tolerance (measured by continuous glucose measurements and daily glucose tolerance tests). Of these four "NAS responders," all demonstrated bacterial taxonomic changes indicative of dysbiosis compared to the "NAS non-responders."

The results of this study (actually multiple studies in one paper!) suggest that consumption of NAS may be another dietary factor contributing to dysbiosis. What is interesting (particularly in the mouse portion of the paper) is the link to impaired glucose tolerance. Most NAS pass through the gastrointestinal tract without being digested by the host and directly encounter the intestinal microbiota. In addition to previous data pointing to weight gain[3] and increased risk of type 2 diabetes[4] in persons consuming NAS, these data provide a compelling argument to counsel our patients to remove NAS from their diet. ■

**Note: A more detailed overview of the mouse data and changes in NAS responder bacterial taxa can be read in the reviewed paper.*

REFERENCES

1. Qin J, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012;490:55-60.
2. Karlsson F, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013;498:99-103.
3. Horwitz DL, et al. Response to single dose of aspartame by NIDDM patients. *Diabetes Care* 1988;11:230-234.
4. Nettleton JA, et al. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* 2009;32:688-694.

PROBIOTICS

Probiotics and the Microbiome

By David Kiefer, MD

Research about the human microbiome and the therapeutic effect of probiotics is changing fast. It can be difficult to know how to counsel our patients about this important topic. The following table is a summary of some of the recent *Integrative Medicine Alert* articles as well as some additional recent intriguing and/or seminal works that, I would argue, should be at your fingertips when the topic comes up with your patients. Consider this a "Part 1." Part 2 will add some of the intriguing results surrounding the prevention and treatment of bacterial vaginosis and candidiasis. Table 1 provides a summary of recent research, with diagnoses (and positive or negative effect), type of study, dosing, species (strains) used, and references, including when the topic was covered in *Integrative Medicine Alert*.

REFERENCES

Aas J, et al. Recurrent *Clostridium difficile* colitis: Case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis* 2003;36:580-585.

Brenner DM, et al. The utility of probiotics in the treatment of irritable bowel syndrome: A systematic review. *Am J Gastroenterol* 2009;104:1033-1049.

Butterworth AD, et al. Probiotics for induction of remission in Crohn's disease. *Cochrane Database System Rev* 2008;(3):CD006634.

Catanzaro R, et al. The gut microbiota and its correlations with the central nervous system disorders. *Panminerva Med* 2014 Nov 12.

Hidding I, Koning C. Probiotics in the prevention and treatment of antibiotic associated diarrhoea. *Agro Food Industry Hi-Tech* 2005;16:18-20.

Kalliomaki M, et al. Probiotics during the first 7 years of life: A cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119:1019-1021.

Kim JY, et al. Effect of probiotic mix (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*) in the primary prevention of eczema: A double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol* 2010;21(2 Pt 2):e386-e393.

Petrof EO, et al. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome* 2013;1:3.

Rajkumar H, et al. Effect of probiotic *Lactobacillus salivarius* UBL S22 and prebiotic fructo-oligosaccharide on serum lipids, inflammatory markers, insulin sensitivity, and gut bacteria in healthy young volunteers: A randomized controlled single-blind pilot study. *J Cardiovasc Pharmacol Ther* 2014 Oct 20.

Ridaura VK, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013;341(6150).

Sazawal S, et al. Efficacy of probiotics in prevention of acute diarrhoea: A meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infect Dis* 2006;6:374-382.

Suez J, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 2014;514:181-186.

Tillisch K, et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013;144:1394-1401.

Tomasz B, et al. Long-term use of probiotics lactobacillus and bifidobacterium has a prophylactic effect on the occurrence and severity of pouchitis: A randomized prospective study. *Biomed Res Int* 2014;2014:208064.

Vilahur G, et al. *Lactobacillus plantarum* CECT 7315/7316 intake modulates the acute and chronic innate inflammatory response. *Eur J Nutr* 2014 Nov 19.

West NP, et al. Probiotic supplementation for respiratory and gastrointestinal illness symptoms in healthy physical active adults. *Clin Nutr* 2014;33:581-587.

Table: Summary of Recent Research on Probiotics and the Microbiome

Diagnosis	Study type	Dose	Species	Reference
Atopic dermatitis prevention	Human RCT	4.8 billion cfu daily	Blend of *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*	Kim, 2010 (*IMA*, February 2012)
Atopic dermatitis prevention	Human RCT	10 billion cfu daily	*Lactobacillus rhamnosus* strain GG ATCC 53103 (mixtures used in other studies)	Kalliomaki, 2007 (*IMA*, February 2012)
Brain effects (less response to negative imagery)	Human RCT	15 billion cfu daily	*Bifidobacterium animalis* subsp *lactis* I-2494, *Streptococcus thermophiles* I-1630, *Lactobacillus bulgaricus* I-1632 and I-1519, and *Lactococcus lactis* subsp *lactis* I-1631	Tillisch, 2013 (*IMA*, February, 2014)
Central nervous system connections with microbiome	Review	N/A (discussed microbiome)	Numerous discussed	Catanzaro, 2014
Clostridium difficile eradication	Case report	N/A (stool transplant)	Numerous species	Aas, 2003; Petrof, 2013
Crohn's, inducing remission (no benefit)	Humans, review	Variety	Several species used in reviewed studies	Butterworth, 2008
Crohn's, prevention of exacerbation	Review	Variety	*Lactobacillus rhamnosus* GG, *Lactobacillus johnsonii*	Jonkers, 2012
Decreased inflammatory response with supplementation	Animal	100 million cfu per kg per day	*Lactobacillus plantarum* CECT 7315/7316	Vilahur, 2014
Diarrhea, acute, treatment	Meta-analysis of 34 studies	Variety	Numerous species	Sazawal, 2006 (*IMA*, February, 2012)
Diarrhea, antibiotic-associated	Review	Variety	*Lactobacillus* species, *Streptococcus* species, *Saccharomyces boulardii*	Hidding, 2005 (*IMA*, February, 2012)
Gastrointestinal (several diagnoses)	Review	Variety (direct fecal delivery discussed)	Numerous species	IMA, July, 2014
Glucose intolerance correlation with artificial sweetener intake	Animal, and human (observational)	N/A: analyzed changes in microbiome	NA	Suez, 2014 (*IMA,* January, 2015)
Irritable bowel syndrome treatment	Humans, review	100000-10 billion cfu daily	*Bifidobacterium infantis* 35624	Brenner, 2009
Lipid improvements with supplementation	Human SBRCT	2 billion cfu daily	*Lactobacillus salivarius* UBL S22	Rajkumar, 2014
Obesity	Animal	N/A (stool transplant)	Numerous species	Ridaura, 2013
Pouchitis, prevention	Human, RCT	3.2-9.6 billion cfu daily	*Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Bifidobacterium bifidus*	Tomasz, 2014 (*IMA*, July, 2014)
Pouchitis, prevention	Review	1800 billion cfus	VSL #3 (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii* subsp. *bulgaricus*)	Jonkers, 2012

DBRCT: double-blind, randomized, placebo-controlled trial; SBRCT: single-blind, randomized, placebo-controlled trial; RCT: randomized, controlled trial; *IMA: Integrative Medicine Alert*

Table 2: Summary of Recent Research on Probiotics and the Microbiome *(cont.)*

Diagnosis	Study type	Dose	Species	Reference
Ulcerative colitis treatment	Review	900-3600 billion cfu	VSL #3 (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*)	Jonkers, 2012
URTI prevention in adults (no effect)	Human DBRCT	10 billion cfu daily	*Lactobacillus acidophilus* NCFM and *Bifidobacterium animalis* subsp. *lactis* Bi-07	West, 2014 (*IMA*, September, 2014)
URTI prevention in adults (positive)	Human DBRCT	2 billion cfu daily	*Bifidobacterium animalis* subsp. *lactis* Bl-04	West, 2014 (*IMA*, September, 2014)

DBRCT: double-blind, randomized, placebo-controlled trial; SBRCT: single-blind, randomized, placebo-controlled trial; RCT: randomized, controlled trial; *IMA: Integrative Medicine Alert*

CME QUESTIONS

1. **Which of the following is true about people 65 years or older who are regular runners?**
   a. Their resting metabolic rate is greater than that of older walkers.
   b. They only walked more efficiently than walkers at 0.75 meters per second.
   c. An age comparison showed that they consume energy similar to young sedentary adults.
   d. A 30% improvement in walking economy was seen.

2. **Supplementation with vitamin D2 has been found to:**
   a. improve survival among children living in Europe.
   b. eliminate colon cancer risk.
   c. be less bioactive and potent compared to vitamin D3.
   d. decrease overall mortality among older adults.

3. **Diversity of gut flora in the Clarke et al study was associated with which of the following?**
   a. Exercise only
   b. Diet only
   c. Both diet and exercise
   d. Neither diet nor exercise

4. **Licorice supports the eradication of *H. pylori* infection:**
   a. when used in substitution for bismuth subsalicylate as a part of a quadruple treatment regime.
   b. when used in substitution for proton pump inhibitors as a part of a quadruple treatment regime.
   c. when used in conjunction with any other pharmaceutical treatments for *H. pylori*.
   d. when used as a solo therapeutic agent.

5. **In a study with healthy volunteers, consumption of non-caloric artificial sweeteners was associated with which of the following?**
   a. Weight loss
   b. Impaired glucose tolerance
   c. Changes in gut microbiota indicative of dysbiosis
   d. Both b & c
   e. All of the above

[IN FUTURE ISSUES]

Dark chocolate and peripheral artery disease

Pistachios and diabetes .

Calcium and vitamin D in the elderly

Aromatherapy

Dear *Integrative Medicine Alert* Subscriber:

Here's a change we know you'll like: From now on, you can earn continuing education credit for each individual issue.

No more having to wait until the end of a 6-month semester or calendar year to earn your continuing education credits or to get your credit letter.

Starting now, you can earn:

- 2.0 *AMA PRA Category 1 Credits*™ for each issue of *Integrative Medicine Alert* and up to 24 total annually.
- 2.0 American Osteopathic Association credits per issue and up to 24 annually

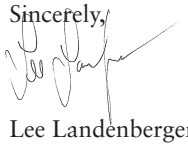
Here's how to do it:

1. Read and study the activity, using the provided references for further research.
2. Until Jan. 4, log on to cmecity.com to take a post-test. First-time users must register on the site using the 8-digit subscriber number printed on your mailing label, invoice or renewal notice. On and after Jan. 5, when logging onto the new AHCMedia.com, go to "MyAHC" and then "My Courses" to view your available continuing education activities.
3. Pass the post-test with a score of 100%; you will be allowed to answer the questions as many times as needed to pass.
4. After completing the test, complete and submit an evaluation form.
5. Once the evaluation is received, a credit letter is emailed to you instantly.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. Our fax is (800) 284-3291 or outside the U.S. at (404) 262-5560. We are also available at customerservice@ahcmedia.com.

Thank you for your trust.

Sincerely,



Lee Landenberger
Continuing Education & Editorial Director