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OBESITY

ABSTRACT & COMMENTARY

The Final Word? Low-carb vs Low-fat

By David Kiefer, MD, Editor

SYNOPSIS: This randomized, parallel group study over 12 months found greater weight and cardiovascular risk benefits in obese adults eating a low-carbohydrate diet vs a low-fat diet.

SOURCE: Bazzano LA, et al. Effects of low-carbohydrate and low-fat diets. *Ann Intern Med* 2014;161:309-318.

The researchers of this randomized, parallel-group trial aimed to address gaps in the literature about so-called "low-carb" (low-carbohydrate) diets, particularly focusing on cardiovascular effects and the effects in a racially diverse population.

The recruitment was from the general population, and, unlike most past research, in people with no comorbidities. Exclusions were cardiovascular disease, type 2 diabetes, kidney disease, surgery, recent weight loss (> 6.8 kg), or the use of prescription weight-loss medications. The 148 participants (51% African American, 88% female, mean age of 46.8 years) were randomized to either a low-carbohydrate group (a diet containing < 40 g per day of digestible, non-fiber carbohydrate) or a low-fat group (a diet of < 30% of total energy intake containing total fat [< 7% saturated fat] and 55% carbohydrate). There were no calorie or energy goals stipulated. Also, participants were asked to not change their exercise amount during the intervention. Each group received the same information about fiber intake (recommended at 25 g daily) and dietary fats (emphasizing monounsaturated fats and avoidance of trans saturated fats).

Each participant received a detailed handbook about food suggestions and recipes for their specific diet. In addition, participants had weekly individual counseling sessions with a dietitian for the first month, then small group sessions every other week for 5 months, and monthly for the last 6 months. One replacement meal (bar or shake) was provided daily for each participant,

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tailored to his/her group assignment.

With respect to data collection, a detailed medical history was obtained from each study participant, and they were asked to do two 24-hour dietary recalls (one weekday and one weekend) at baseline, and 3, 6, and 12 months in order to calculate dietary nutrient intakes. The researchers measured body weight and height, body composition, blood pressure, and collected urine and blood (lipids, C-reactive protein, glucose, creatinine, insulin).

At baseline, participants in the two groups were similar across all of these measurements, except for the parameters listed in Table 1.

Of the 148 people randomized at the beginning of the study (73 in the low-fat diet group and 75 in the low-carbohydrate group), 60 and 59, respectively, were assessed at the end of the 12 months, though all 148 participants were included in an intention-to-treat data analysis. At the end of 12 months, as expected, the low-fat diet group consumed higher amounts of carbohydrates and lower amounts of proteins and fats ($P < 0.001$). The researchers stated that "Physical activity amounts were similar throughout the study," but it is unclear if this refers to baseline vs 12 months, or between the two diet groups. The total calorie consumption was similar between the two groups over the course of the study.

Compared to baseline, people on the low-carbohydrate diet lost 3.5 kg more weight over 12 months than people on the low-fat diet ($P = 0.002$). Also, the low-carbohydrate group gained 1.7 kg lean mass ($P = 0.003$), lost 1.5 kg fat mass ($P = 0.011$), increased HDL 6.9 mg/dL ($P < 0.001$), decreased triglyceride 14.2 mg/dL ($P = 0.038$), decreased total-HDL ratio 0.44 ($P = 0.002$), and decreased C-reactive protein 15.2 nmol/L ($P = 0.024$). Overall, the low-carbohydrate diet group lowered their 10-year Framingham risk 1.4 points compared to the low-fat group ($P < 0.001$). There were no changes in waist circumference, total cholesterol, LDL cholesterol, blood pressure, glucose, serum insulin, nor serum creatinine.

Symptoms that developed over the course of the study were similar between the two groups except for more headaches reported in the low-fat diet group ($P = 0.03$). No serious adverse effects were reported.

■ COMMENTARY

There are several compelling aspects to this study. Few other studies have analyzed a racially diverse population, in this case 51% African American. Too often, clinicians are left speculating about how to extrapolate research results from a predominantly white study population to their patient demographic. Also, this study included people who were obese but otherwise healthy, allowing the results to be an important commentary on the possible preventive aspect of the dietary change, again a relatively unique aspect to this research thread.

The benefits of the low-carbohydrate diet in this population were clear; numerous significant changes in laboratory tests were seen, including an

Table 1. Baseline Characteristics Differing Between the Low-carbohydrate and Low-fat Diet Groups

Measurement	Low-carbohydrate Diet Group	Low-fat Diet Group
Serum cholesterol (md/dL)	198.8	204.3
Serum triglyceride (md/dL)	112.6	125.5
Serum creatinine (micromol/L)	88.4	97.2
Mean physical activity level (MET-hours/week)	16.3	19.6

Summary Points

- In a racially diverse obese population, people on a low-carbohydrate diet for 12 months were better able to lose weight than those on a low-fat diet.
- The low-carbohydrate diet also lowered cardiovascular risks more than the low-fat diet.

increased HDL, otherwise a difficult laboratory test to budge. With a movement away from "number chasing" in recent guidelines, it is good to also see that overall risk via the Framingham also showed a concrete benefit.

It could be argued that a 3.5 kg (almost 8 pounds) weight loss over 1 year is negligible, but it should be mentioned that this was in the context of stagnant exercise amounts and no limit on calorie intake. It makes one wonder what could have been accomplished by a shift in those other variables too.

Did the baseline inter-group differences (*see Table 1*) affect the final results? Ideally, the two groups would have been identical at baseline, but this was not the case and it brings up some questions. The people in the low-carbohydrate diet group were less active, but had better lipid profiles, than the low-fat diet group. If the lipid profile is representative of metabolic (dys)function, then it could be argued that it would have been even more difficult to shift any of the measurements in the low-carbohydrate diet group, starting as it was at baseline better than the low-fat diet group. This, then would strengthen the findings. However, less activity may indicate that the low-carbohydrate diet group had "wiggle room" in affecting insulin sensitivity, making it more likely that dietary change would shift physiology, and, therefore, weight and cardiovascular risks. If future, larger trials can increase numbers and random sampling to even the initial playing field, then these methodological issues will be addressed.

How difficult would it be to implement this dietary change in the "real world"? The low-carbohydrate goal of < 40 g on non-fiber carbohydrate is truly low. Many people consume 200+ g of fiber and non-fiber carbohydrate a day, so the study diet would be a significant change from normal. Adding to this reality check, it helps to view this study's diets in context of some other well-known dietary guidelines (*see Table 2*). Also, this study had a high completion rate (about 80%), higher than most other comparable studies, which was almost certainly due, in part, to the many individual and group counseling sessions. Such an intensive effort is usually beyond what clinics can offer their patients. Perhaps the most useful part of these results is to serve as a benchmark for which people can aim, a goal to shoot for, an ideal that gives them hope that their efforts at dietary change do, in fact, matter.

Interestingly, as much as the literature supports a connection between weight and risk for diabetes, no changes were seen here in serum glucose nor insulin, recognizing that this study population was disease free. It would have been useful to follow this cohort longer and analyze for incidence of diabetes; would the weight loss and metabolic changes translate into improvements in diabetes risk as well?

In the context of cardiovascular risk and obesity, this study is yet another strong indication that carbohydrates, rather than fats, should be the focus when it comes to treating or preventing obesity. In general, there seems to be little reason to recommend a low-fat diet in this population, and many (more) reasons now to help our patients to avoid non-fiber carbohydrates. ■

Table 2. Comparison of Daily Nutrient Intakes Between the Groups in this Study with Three Other Well-known Nutritional Guidelines

	This Study: Low-Carbohydrate	This Study: Low-Fat	USDA 2005 Food Pyramid[1]	MyPlate (based on the 2010 Dietary Guidelines for Americans)[2]	Ornish Spectrum Diet[3]
Carbohydrate	< 40 g non-fiber	55% of daily calories		3 oz of whole grains daily	
Fat		< 30% of daily calories	20-35% of daily calories		< 10% of daily calories
Protein				5-5.5 oz	

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CANCER

ABSTRACT & COMMENTARY

Red Meat and Increased Breast Cancer Risk

By Traci Pantuso ND, MS

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

SYNOPSIS: In this study, the authors investigated the relationship between dietary protein sources during early adulthood in women and overall breast cancer risk. Previously, Cho and colleagues reported that increased red meat intake was associated with greater risk of breast cancer in premenopausal women who participated in the Nurses' Health Study II (NHII) cohort. The current study found that red and processed meat intake in early adulthood may increase the risk of breast cancer in women, but eating legumes, nuts, poultry, and fish reduced the risk of breast cancer in the NHII cohort.

SOURCE: Farvid MS, et al. Dietary protein sources in early adulthood and breast cancer incidence: Prospective cohort study. *BMJ* 2014;348:g3437.

The majority of the research has demonstrated no significant association between breast cancer and red meat intake, but most of these studies examined meat intake at midlife, not in early adulthood when environmental cancer pathophysiology may occur.[1] Red and processed meat intakes have been associated with an increasing risk of colorectal, esophageal, liver, and prostate cancers, but not breast cancer.

Summary Points

- According to this study, each daily serving of red meat increased relative risk of breast cancer by 13%.
- Higher poultry intake is associated with a lower incidence of breast cancer in postmenopausal women.
- Replacing one serving per day of red meat with a combination of poultry, legumes, fish, eggs, and nuts reduces the relative risk of breast cancer.

METHODS

The study population was the Nurses' Health Study II, a prospective cohort study that started in 1989; participants included 116,430 female nurses who were aged 24-43 years old in 1989. A food frequency questionnaire (FFQ) was given in 1991 regarding their dietary intake in the past year. A total of 97,813 women answered the questionnaire; 9010 women were excluded from the study, meaning that data came from a total of 88,803 women. Exclusion criteria included the following:

- Diagnosis of diabetes, coronary heart disease, or stroke
- Diagnosis of any cancer other than non-melanoma skin cancer
- Missing data on red meat intake or age
- Being postmenopausal
- 70 or more of the FFQ items were left unanswered
- Dietary intake that was < 2508 kJ (599 kcal) or ≥ 14,630 kJ (3496 kcal)

DIET EVALUATION

In 1991, 1995, 1999, 2003, and 2007, participants completed a semi-quantitative FFQ that evaluated usual dietary intake and alcohol use in the past year. Items related to red meat that were evaluated consuming either unprocessed red meat (beef, pork, or lamb as a sandwich, pork as a main dish, beef or lamb as a main dish, and hamburger) or processed red meat (hot dogs, bacon, and other processed meat such as sausage). Other protein sources such as eggs, poultry, legumes, and nuts were also measured.

Food intake measured in 1998 included an assessment of foods that were consumed during

Table 1. Percent Increased Breast Cancer Relative Risk by Group

	% Increased Risk per Additional Serving of Red/Processed Meat	RR	95% CI
All women	13	1.13	1.04-1.22
Premenopausal women	12	1.12	1.01-1.25
Postmenopausal women	8	1.08	0.94-1.23

1960-1980 when these women would have been in high school. Nutrient intakes were calculated by multiplying the frequency of consumption of each item by the nutrient content of the reported portion sizes and then adding up the items. Nutrient values were taken from the USDA, food manufacturers, independent academic sources, and investigators' own fatty acid analysis for commonly used products.

BREAST CANCER MEASUREMENT

Breast cancer cases were evaluated based on the biennial questionnaires with hospital and pathology reports when available. Eighty-eight percent of medical records were obtained and 98% of self-reported breast cancer cases were confirmed through review of pathology reports. Cases of carcinoma in situ were excluded from the analysis. Estrogen and progesterone receptor status was determined by the pathology reports.

Additional variables measured included:

- Age, height, weight, smoking status
- Family history of breast cancer, history of benign breast disease
- Age at menarche, oral contraceptive use
- Parity, age at first birth
- Menopausal status, postmenopausal hormone use, and age at menopause.

According to food group or nutrient intake, women were divided into five categories from highest to lowest dietary intakes. Cox proportional hazards models were used to calculate relative risk and 95% confidence intervals (CI). To assess interactions with additional variables, multivariate analysis was performed.

RESULTS

Between 1991 and 2011, a total of 1,725,419 person years data from 88,803 premenopausal women was obtained, and 2830 invasive breast cancer cases were identified, including:

- 1511 premenopausal breast cancers
- 918 postmenopausal breast cancers
- 401 cancers in women of uncertain menopausal status.

The average age of the participants in 1991 was 36.4 years, with a range of 26-45 years. The average age of diagnosis in premenopausal women was 45, with a range of 27-60 years. In postmenopausal women, the average age was 55 with a range of 39-64 years.

Women in the highest red meat quintile had a median intake of 1.5 serving/day compared to women in the lowest quintile who had a median intake of 0.14 serving/day.

Women in the highest red meat quintile demonstrated a 22% increased relative risk (RR) of breast cancer compared to women with the lowest intake (RR, 1.22; 95% CI, 1.06-1.40; P_{trend} = 0.01 for highest quintile vs lowest). After controlling for total fat intake, the relative risk was still significant (RR, 1.20; 95% CI, 1.03-1.40; P_{trend} = 0.04). Women who had a median intake of 1.5 serving/day of red meat compared to those that had 0.14 serving/day had a 22% increased relative risk of breast cancer with each additional daily serving of red meat increasing the relative risk of breast cancer by 13% (RR, 1.13; 95% CI, 1.04-1.22; *see Table 1*).

Red meat intake during adolescence did not appreciably change the relative risk of breast cancer overall (RR, 1.20; 95% CI, 1.07-1.34) or the risk of premenopausal breast cancer (RR, 1.24; 95% CI, 1.07-1.44). With additional adjustment for menopausal status, oral contraceptive use, body mass index, smoking, height, age at menarche, age at menopause, parity and age at first birth; red meat intake during adolescence changed little for breast cancer overall (RR, 1.18; 95% CI, 1.06-1.33) and for premenopausal breast cancer (RR, 1.20; 95% CI, 1.03-1.40).

The study also found that women who consumed more red meat had higher energy intake, were heavier, were more likely to smoke, and were more likely to have three or more children. These women were also less likely to use oral contraceptives and to have a history of benign breast disease. The authors controlled for these findings through their multivariate statistical model with additional adjustments for these potential confounders.

Eating poultry was associated with a lower risk

of postmenopausal breast cancer (RR, 0.73; 0.58-0.91; P_{trend} = 0.02) and the estimate was unchanged when adjusted for fruits, fat, or vegetable intake. The cumulative average intake of poultry by premenopausal women was associated with a lower relative risk of postmenopausal breast cancer. There was a 25% lower risk of postmenopausal breast cancer per serving of poultry/day (RR, 0.75; 95% CI, 0.58-0.98).

Legume, fish, egg, and nut intakes were not associated with either post- or premenopausal breast cancer risk. Replacing one serving per day of red meat with a combined serving of legumes, nuts, poultry, and fish reduced the relative risk of breast cancer in women overall.

■ COMMENTARY

Breast cancer is the second leading cause of cancer in the U.S. population and the number one cause of cancer in women. During 2014, 232,670 new cases are expected and 40,000 deaths are expected to be due to breast cancer in the United States.[2] In addition, 12.3% of women in the United States are expected to receive a diagnosis of breast cancer during their lifetime.[2] This study found that a median intake of 1.5 servings of red meat per day had a 22% increased relative risk of breast cancer compared to women with the lower intake of 0.14 serving/day. Each additional serving of red meat increased the relative risk of breast cancer another 13% in women. Because of the high incidence of breast cancer, dietary intake of red and processed meats may be a significant risk factor and is also a modifiable factor.

The strengths of this study are the number of participants, the large number of breast cancer cases and the long follow-up period. There are a number of limitations to this study. The study population was predominately white educated women from the United States, making the conclusions less generalizable to other populations. Another limitation with this study is that genetic predispositions such as breast cancer gene (BRCA) mutations were not measured and have been shown to increase overall breast cancer risk in women. Exercise was also not measured in this study, a clear and proven variable in breast cancer risk. Another limitation of this study is that risks related to unprocessed meat servings were calculated together rather than evaluated individually, and the chemicals in processed meat may have been an important contributing factor to breast cancer development. Nitrites and nitrates are used to preserve processed meats and can undergo a process of nitrosation, which occurs spontaneously with these compounds. The resulting compounds have been declared to be "probable human carcinogens" by the International Agency for Cancer Research in 1996.[3]

Despite the limitations of this study, the increased relative risk of breast cancer with red meat intake in women is notable and also modifiable. Although there is not a larger body of evidence suggesting that increased red meat intake increases relative risk of breast cancer, there is evidence for increased risk of colorectal, esophageal, liver, and prostate cancer.[3] All of these are compelling reasons to pay attention to this aspect of someone's diet. It is also recommended to encourage patients to eat red meat products that are procured from grass-fed animals without additional hormones and to avoid processed meats that contain chemicals such as nitrites.

CONCLUSION

Recommending a diet such as the Mediterranean diet pattern that is low in red meat emphasizing vegetables, fruit, legumes, and healthy fats with poultry is a reasonable recommendation to reduce the risk of cancer and promote overall health.[4,5] ■

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ABSTRACT & COMMENTARY

The Yellow Spice That Just Keeps on Giving: Turmeric and Arthritis

By David Kiefer, MD, Editor

SYNOPSIS: A polysaccharide-rich extract of turmeric rhizome provided benefits in people with knee osteoarthritis.

SOURCE: Madhu K, et al. Safety and efficacy of *Curcuma longa* extract in the treatment of painful knee osteoarthritis: A randomized placebo-controlled trial. *Inflammopharmacology* 2013;21:129-136.

This was a randomized, single-blind (the study investigator was not blinded to the group assignment), placebo-controlled trial examining the effects of a curcuminoid-free extract of turmeric (*Curcuma longa*, Family Zingiberaceae) rhizome on adults with knee osteoarthritis (OA). The authors wished to expand on turmeric research by studying the polar, polysaccharide-rich fraction of this rhizome. Whole turmeric contains many phytochemicals, including curcuminoids and polysaccharides; the anti-inflammatory effects of turmeric may have its origins in a compound other than the oft-studied curcuminoids.

Summary Points

- A polysaccharide component of turmeric rhizome, in the form of the extract HR-INF-02, was studied in 120 people with moderate osteoarthritis in a placebo-controlled, four-arm, 42-day study.
- The group taking only turmeric had better improvements, when compared to placebo, in pain severity, the WOMAC index, and the Clinician Global Impression of Change.
- The turmeric group also experienced less side effects over the course of the research study.

To be included in the trial, study participants had to be older than the age of 40 and have "clinical evidence" documenting knee OA, including pain on most days for the 6 months preceding the trial and radiological evidence of grade 2-3 OA (Kellgren and Lawrence OA rating system, from 1 [minimal] to 4 [severe] OA). Exclusion criteria were trauma or surgery to the affected knee(s), patellofemoral disesase, medical or arthritic conditions affecting knee evaluation (not specified), or any disease that may affect a participants ability to finish the trial (again, not specified).

The study participants were randomized to one of four groups (*see Table 1*). The doses for the turmeric and glucosamine were based on animal and human research as cited by the authors.

The researchers collected demographic, medication, and past medical history information. The primary outcome was OA pain severity as per the visual analog scale (VAS) rated 0-100 at baseline, day 21, and day 42. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) (24 questions, each rated 0-4, total

Table 1. Four Groups of *Curcuma longa* Research Study

Group	Substance	Dose	Number of Participants
Placebo	Microcrystalline cellulose	400 mg twice daily	30
Turmeric	Extract HR-INF-02 gelatin capsules containing 12.6% polysaccharides	500 mg twice daily	30
Glucosamine	Glucosamine sulfate	750 mg twice daily	30
Glucosamine + Turmeric	As above	500 mg twice daily (turmeric) plus 750 mg twice daily (glucosamine)	30

possible 96) was used to assess pain, stiffness, and functional limitation of the affected joint. In addition, the Clinician Global Impression of Change (CGIC) on days 21 and 42 assessed the study participants' overall condition. Participants were allowed acetaminophen up to 4 g daily as rescue medication, though not within 24 hours of an examination.

An intention-to-treat analysis of the 120 patients randomized in the trial found that all groups improved in VAS, WOMAC, and CGIC over the course of the 42 days ($P < 0.01$), but the turmeric only group fared better than placebo ($P < 0.05$) for all three scales. Turmeric alone was better than the combination for VAS and WOMAC ($P < 0.05$), and better than glucosamine only for CGIC ($P < 0.05$). Furthermore, only four participants in the turmeric group complained of joint pain at the end of the trial (compared to 29 at the beginning) and fewer participants in the turmeric group used rescue medication; both of these results were noted by the authors to be statistically different from the other groups ($P < 0.01$). The turmeric group and the combination group had less joint crepitus, and all treatment groups had less joint effusion and joint limitation when compared to placebo.

Thirteen mild adverse effects were reported, the least number (n = 2) being in the turmeric group. The authors did not run statistics on the adverse effect spread.

■ COMMENTARY

Turmeric is becoming standard of care in the integrative medicine and nutraceutical worlds as a treatment for pain, including pain from osteoarthritis.[1] Most plants have a variety of phytochemicals accounting for their physiological activity, and turmeric is no exception. A group of compounds in turmeric, the curcuminoids, including curcumin, have been studied for their anti-inflammatory effects,[2] but the trial being reviewed here sheds light on similar anti-inflammatory, pain-relieving activity for the polysaccharide component delivered in the extract HR-INF-02.

Some questions surface upon further review of this article. Some of the results seem too good to be true. Turmeric was the best performer and the intervention with the least side effects. Was it due to the turmeric extract company's involvement? The company donated the turmeric extract, but it does not seem to have been involved in the data collection or analysis. A statement to that effect would have been nice to see. Also, improvements in the three scales were seen at 21 and 42 days, not only for turmeric, but also for glucosamine, an intervention that normally takes longer before an effect is seen.[3] Could some of these substantial effects be due to the single-blind nature of this trial? Possibly, as subtle interactions between staff and participants could lead to clinically relevant benefits. Corroboration with a longer, larger trial conducted in a double-blind fashion would do much to address these criticisms and bring this curcuminoid-free extract, or extracts that contain both curcuminoids and polysaccharides, into greater use. ■

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VITAMIN D

ABSTRACT & COMMENTARY

To D or Not to D?

By Allan J. Wilke, MD, MA

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

This article originally appeared in the May 29, 2014 issue of **Internal Medicine Alert.**

SYNOPSIS: The American Geriatrics Society has published guidelines on the use of vitamin D supplementation for the prevention of falls in the elderly, but some researchers are not on board with this.

SOURCE: American Geriatrics Society workgroup on vitamin D supplementation for older adults. Recommendations abstracted from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences. *J Am Geriatr Soc* 2013; Dec. 18. doi: 10.1111/jgs.12631. [Epub ahead of print].

This summary condenses the efforts of the American Geriatrics Society (AGS) workgroup on vitamin D supplementation for the elderly into what the workgroup imagined would be bite-size, digestible nuggets for primary care providers (PCPs). It is a very dense report. The entire 38-page document is available for sale.[1] [*Disclaimer: I am a member of AGS, but did not have a hand in the development of these guidelines.*]

The recommendations begin with a brief review of how vitamin D is made. It is synthesized in the skin by way of exposure of cholesterol to ultraviolet B light, hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D], and then hydroxylated again to 1,25-dihydroxyvitamin D (D3). We get our vitamin D through sun exposure, by way of supplements, and through eating foods that are fortified with vitamin D.

The overall goal of the recommendations is to reduce injuries from falls attributable to low serum vitamin D levels. To achieve that goal, the workgroup reviewed the literature through 2010 and formulated six objectives:

- Develop clinical guidelines that address vitamin D intake from all sources.
- Set goals for 25(OH)D levels that correlate with reduced risk of falls and injuries, while avoiding toxicity.
- Strategize on how to obtain those levels.
- Develop clear guidelines for PCPs.
- Define at-risk groups of the elderly.
- Rate the various ways vitamin D levels are measured.

The recommendations are as follows: Every community dwelling senior (i.e., ≥ 65 years) and institutionalized older adults should be supplemented with at least 1000 international units (IU) daily. This should always be coupled with calcium (Ca++) supplementation; however, the workgroup did not specify an amount of Ca++. It did note that vitamin D doses < 600 IU do not prevent falls, and Ca++ doses in the studies reviewed were commonly 1000-1200 mg daily. Supplementation of an institutionalized older adult should be with a dose of vitamin D ≥ 1000 IU/d, plus Ca++.

Serum 25(OH)D levels should be > 30 ng/mL (75 nmol/L). The best way to achieve this is by reviewing all sources of vitamin D and keeping the total at 4000 IU. The authors include a table for individualizing the dose based on food intake, multivitamin use, unprotected sun exposure, obesity, and skin pigmentation. Individuals taking medications that bind vitamin D or increase its metabolism or have malabsorption syndromes may need their doses tweaked.

Summary Points

- The American Geriatrics Society reviewed the vitamin D literature through 2010 with the overall goal of reducing injuries from falls due to low serum vitamin D levels.
- All institutionalized older adults should be supplemented with 1000 IU vitamin D plus calcium (dose not specified); vitamin D3 is preferable to vitamin D2.
- Serum 25-hydroxyvitamin D should be > 30 ng/mL.

Routine measurement of 25(OH)D serum levels isn't necessary before beginning supplementation, nor after for monitoring, unless you are outside the recommended dose. If you decide to monitor anyway, wait until 4 months and measure at the midpoint between doses. You might want to monitor the people who show up in the table.

Vitamin D is available as ergocalciferol (D2) by prescription and cholecalciferol (D3) over-the-counter, and either form may be used. Vitamin D3 is derived from animal sources, possibly a problem for vegetarians. They differ in their pharmacokinetics; the maximal dosing interval for vitamin D2 is 2 weeks and vitamin D3 is 4 months. Because of its long dosing interval, vitamin D3 can be given daily, weekly, or monthly.

There were a number of warnings and "don't do this" statements. Don't prescribe once-yearly doses of either to get a patient through the winter. Don't use combination vitamin D/Ca++ tablets as the primary source of vitamin D, because the doses of vitamin D are too small and the tablets need to be dosed daily. The combination of a daily vitamin D/Ca++ tablet and a monthly vitamin D capsule may be a good compromise. Don't rely on cod liver oil, because of the risk of vitamin A toxicity

at the dose needed for adequate vitamin D. Taking vitamin D with meals that contain oil is good; taking vitamin D with cholestyramine and high-fiber foods or supplements is not.

■ COMMENTARY

One thing I like about these recommendations is that the goal was outcome-based (preventing injuries), rather than biochemically based. However, before adopting these guidelines, please read the following.

Things got a little murky in late 2013 and early 2014 with the publication of four systematic reviews/meta-analyses and one study. Powe and colleagues' study noted the paradox of black Americans consistently having lower levels of total 25(OH)D than whites, while having higher bone mineral density (BMD) and a lower risk of fragility fractures.[2] These researchers measured levels of total 25(OH)D, vitamin D-binding protein, the parathyroid hormone, and BMD. They discovered that the average levels of both total 25(OH)D and vitamin D-binding protein were lower in blacks than in whites and concluded that the bioavailable vitamin D are similar. This study was followed by a systematic review of articles that measured the effect of 25(OH)D concentrations on non-skeletal health outcomes in adults.[3] The authors concluded, "Supplementation in elderly people (mainly women) with 20 µg [note: equivalent to 800 IU] vitamin D per day seemed to slightly reduce all-cause mortality," and speculated that low levels of vitamin D were not the cause of illness, but the result of inflammatory processes and a marker of illness.

Then, in April, came three articles. In the first two, published in *BMJ* on April 1, both systematic reviews and meta-analyses, Chowdhury et al concluded that vitamin D3 (but not vitamin D2, which may make things worse) supplementation "significantly reduces overall mortality among older adults," but cautioned against widespread supplementation.[4] Theodoratou et al concluded that there is no highly convincing evidence of a clear role of vitamin D for any outcome.[5] I do not think that *BMJ* publishes an April Fools' edition. You could argue that these two meta-analyses took on the very broad effects of vitamin D on health in general, and the AGS guidelines are focused on preventing falls in the elderly. You could argue that, except for the most recent April article, a trial sequential analysis by Bolland et al[6] which asserts that vitamin D does not reduce falls by 15% or more (the risk reduction threshold they set before they conducted the analysis) and thus, there is little reason to prescribe vitamin D.

This is exasperating! My advice? First, do no harm. If you want to prescribe vitamin D, follow the AGS's guidelines and avoid poisoning your patients. Use vitamin D3 because it's cheap, it may be safer than vitamin D2, and you can space out the doses. If you don't want to, you have several meta-analyses to back you up. ■

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SHORT REPORT

Amide Form of N-acetylcysteine Improves Outcomes in Experimental TBI

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

SYNOPSIS: Mitochondrial oxidative stress and damage is connected to neuronal cell death and behavioral outcomes after TBI. Antioxidant treatment with the amide form of N-acetylcsyteine, which has central nervous system (CNS) bioavailability, was shown to improve markers of damage and cognitive function in rats when provided by intraperitoneal injection post experimental TBI.

SOURCE: Pandya JD, et al. N-acetylcysteine amide confers neuroprotection, improves bioenergetics and behavioral outcome following TBI. *Exp Neurol* 2014;257:106-113.

Traumatic brain injury (TBI) has been shown to lead to both rapid and prolonged mitochondrial disruption that overwhelms antioxidant systems. N-acetylcysteine (NAC), an antioxidant that is a precursor to glutathione (GSH), has been shown to improve mitochondrial function by increasing GSH levels after TBI. Increased cellular and mitochondrial permeability with a lipid soluble and neutrally charged amide form of NAC (NACA) improves CNS bioavailability of the molecule and may offer improved benefits.

A rat study, with experimenters blinded to treatments, assessed markers of cognitive function, cortical tissue, oxidative stress, mitochondrial respiration, and GSH levels in animals subjected to experimental TBI that were subsequently given intraperitoneal injections of NACA, NAC, or placebo vehicle. Comparisons with the non-amide form of NAC were only made in assessment of the cortical tissue sparing and cognitive function. To assess cortical tissue sparing, cognitive function, and oxidative stress, intraperitoneal injections of a NACA (or NAC) bolus of 150 mg/kg in a vehicle solution were provided at 30 minutes post-injury. To assess mitochondrial respiration and GSH content, intraperitoneal injections of a NACA bolus containing 150 mg/kg in a vehicle solution were provided at 5 minutes and 6-hour intervals up to 24 hours post-injury. All treatments were compared to treatment with the vehicle solution.

NACA was shown to significantly improve cognitive function (water maze learning ability) between 11 and 14 days post-TBI and treatment compared to both NAC and vehicle. Cortical tissue, evaluated at 15 days, was significantly spared with NACA treatment compared to treatments with both vehicle and NAC. Treatment with NAC was not observed to have any effect on cortical tissue or cognitive function. Oxidative stress, measured by lipid peroxidation, in rats treated with NACA was significantly decreased at 7 days post-TBI. Finally, mitochondrial respiration and total and reduced GSH content were significantly improved with NACA treatment at 25 hours post-injury with no significant difference from that of uninjured (untreated) animals. In contrast, rats treated with only the vehicle solution experienced significant decreases in each of these measures. These dosages are comparable to that utilized for acetaminophen toxicity in the United Kingdom, for which the treatment is intravenous NAC at a dosage of 150 mg/kg in the first 15-60 minutes, followed by lower doses through the initial 20-hour period. NACA (the amide form of NAC) is a relatively new formulation (2000s) of NAC, and is not the same as what is traditionally used in practice. ■

Summary Point

- The amide form of N-acetylcysteine was shown to improve cognitive function, lower oxidative stress markers, and spare cortical tissue after traumatic brain injury (TBI) when given by intraperitoneal injection to rats at a dose of 150 mg/kg at time intervals ranging from 5 minutes through 24 hours post injury.

CME INSTRUCTIONS

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CME QUESTIONS

1. **In the study by Bazzano et al, the low-carbohydrate diet group demonstrated which of the following when compared to the low-fat diet group?**
   a. Increased HDL
   b. Increased CRP
   c. Increased Framingham risk
   d. Increased total-HDL ratio

2. **Choice of dietary protein intake may be an important factor in reducing the relative risk of overall breast cancer. According to this study, which dietary proteins should be recommended to reduce relative risk of breast cancer?**
   a. All dietary proteins are equal in conferring an increased relative risk of breast cancer.
   b. Red meat consumption does not increase the relative risk of breast cancer.
   c. Poultry consumption is associated with a lower relative risk of breast cancer.
   d. Poultry consumption increases the relative risk of breast cancer.

3. **Which of the following interventions provided the best improvements in pain severity, the WOMAC index, and the Clinician Global Impression of Change (CGIC) over 42 days when compared to placebo?**
   a. 500 mg twice daily curcuminoid-free turmeric extract
   b. 750 mg twice daily glucosamine sulfate
   c. 500 mg twice daily curcuminoid-free turmeric extract PLUS 750 mg twice daily glucosamine sulfate
   d. placebo

4. **Choose the correct recommendation from the American Geriatrics Society for prescribing vitamin D supplementation.**
   a. Vitamin D supplementation should always be coupled with calcium supplementation.
   b. Every community-dwelling senior should be supplemented with at least 1000 mg daily.
   c. Never begin supplementation of vitamin D without first measuring 25(OH)D serum levels.
   d. Vitamin D2 is favored because it is more effective than vitamin D3.
   e. Because of its long dosing interval, vitamin D3 can be given yearly.

5. **Intraperitoneal treatment with an amide form of N-acetylcysteine post experimental TBI has been shown in an animal study to:**
   a. improve cognitive function but not oxidative stress or mitochondrial respiration.
   b. improve oxidative stress markers, but not cognitive function.
   c. improve cognitive function, oxidative stress markers, mitochondrial respiration, and glutathione levels.
   d. improve mitochondrial respiration and glutathione levels but not cognitive function.

[IN FUTURE ISSUES]

Subclinical hypothyroidism: Herbs and food

Testosterone supplements

Exercise and gut microbiota