

Integrative Medicine

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

CARDIOVASCULAR DISEASE

Calcium and Cardiovascular Risk Updates: The Bare Bones

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

Calcium is a well-known, little-maligned substance that has a long and important history in terms of health and disease. Interestingly, it is the fifth most common mineral on Earth, and is a vital component of both plant and animal life. Although nearly all the calcium in the body (> 99%) is retained in the bones and teeth, it plays a significant role in the function and diseases of the muscles (skeletal and smooth), nerves, cardiovascular, gastrointestinal, and renal systems. As a nutrient, it is one of the most recognized by the public for its use for osteoporosis and bone health, where it continues to be a grade A evidence-based recommendation for healthy bones when accompanied by exercise.¹ However, its association with cardiovascular disease risk is a more recent example of the growing understanding of calcium's role in our health. A number of recent updates over the past year (cardiovascular disease risk in particular) are noteworthy.

BRIEF HISTORY AND BACKGROUND

Osteoporosis (from the Greek word for “porous bones”) is the most commonly recognized disease associated with calcium deficiency and poor absorption/malnutrition. Long recognized by anthropologists who studied the remains of ancient civilizations, these early observations showed that loss of bone density and other associated structural changes were the first associations between chronic malnutrition and osteoporosis.² However, it wasn't until the mid-20th century that Fuller Albright, MD, made the link between a postmenopausal state and osteoporosis from a modern medical standpoint (hence, the Fuller Albright Award, which has been presented by the American Society for Bone and Mineral Research every year since 1981). Subsequently, bisphosphonate medications were discovered in the 1960s to help minimize osteoclast destruction of the skeletal system.

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Summary Points

- Calcium is an essential part of a healthful diet, and research updates in the past year confirm recommendations that adults receive 1,000 mg per day.
- Serum vitamin D levels in the range of 40-80 ng/mL promote and are essential for efficient calcium absorption in the gut.
- From a cardiovascular perspective, calcium supplementation is safe, but excessive doses (> 2,500 mg per day) should be avoided, particularly among men and women with active cardiovascular disease and increased cardiovascular risk factors.
- Caution should be used in elderly women with history of stroke because of the increased risk of dementia by avoiding excessive calcium intake (> 1,000 mg/day).
- Calcium supplement selection should be based on cost, accessibility, and patient preference, noting that most forms of calcium supplements are absorbed relatively equally as long as it is taken with food at ≤ 500 mg at different times of the day.

Although calcium plays a role in nearly every aspect of human metabolism, 99% of calcium deposits reside in the bones and teeth. However, with age — as well as with a host of other health problems, including alcoholism, anorexia, tobacco use, hyperthyroidism, malnutrition, and kidney disease — bone density decreases through a combination of accelerated bone loss and decreased bone repair. Women are most at risk because of lowered levels of estrogen after menopause. For these reasons, osteoporosis remains the top cause of bone fracture in the elderly.³

Although the underlying pathophysiology and risks associated with osteoporosis are relatively well understood, many questions remain in terms of prevention and treatment of advanced disease.

CALCIUM AND THE HEART

It would seem a simple conclusion that if osteoporosis and its sequelae are characterized by loss of bone mineralization (calcium in particular), then the logical solution would be to consume more calcium. However, like many things medical, it hasn't been that straightforward.

For the past several decades, the standard recommendation for women of all ages has been to consume higher amounts of calcium, but research has been mixed regarding benefits in preventing and treating osteoporosis and osteopenia. Furthermore, the question of harm increasingly has come into play, with a body of literature revealing an association between coronary artery

calcium deposition and cardiovascular disease.

Since the early days of X-ray technology, arterial calcium deposits have been observed. In the 1950s, when heart disease became more recognized as a significant cause of mortality in the United States, the association between arterial calcium and cardiovascular disease became more widely known, thanks to numerous publications about the growing ability to detect these calcifications with radiography.⁴

Fast-forward to today: Advances in CT technology using 256- and 320-slice scanners have led to the development of sensitive and accurate arterial calcium scoring in preventive cardiology, which is now used to help make treatment decisions for patients who have or are at risk for heart disease. This technological advancement is helpful in a clinical setting, given the fact that catheter-based angiography is expensive and carries some risk of serious complications because of its invasive nature (the more invasive the procedure, the higher the risks). From a risk/benefit perspective, up to half of all elective catheter-based interventions reveal no or insignificant coronary artery disease.⁵ Although it is now clear that calcium is a marker for diseased arteries,⁴ how and when to use this technology and how to interpret it clinically remain unclear. The United States Preventive Services Task Force concluded that the evidence currently is insufficient to fully assess the benefits and harms of coronary artery calcification scoring.⁶ From a cardiology perspective, CT

angiography is a helpful tool in determining appropriate care and treatment in symptomatic patients who are at intermediate risk for coronary artery disease.⁷

DO NO HARM

The question then looms, to what extent (if at all) does dietary/supplemental calcium intake factor into the risk/benefit discussion for 1) treating/preventing osteoporosis, and 2) contributing/advancing cardiovascular disease? This is especially pressing given that the top cause of death among women in the United States is heart disease (22.4%), while unintentional injuries (falls, fractures) ranks sixth at 3.8%.⁸

Although calcium remains a top-tier, grade A evidence-based part of osteoporosis treatment, questions have emerged regarding the possible contribution to coronary calcium deposits and advancing coronary artery disease. Three studies published in 2016 shed more light on the conflicting evidence regarding potential cardiovascular risks associated with high levels of calcium intake. The first by Chung et al reanalyzed two separate systemic reviews to examine the effects of supplemental calcium ingestion on cardiovascular disease among healthy adults.⁹ The study authors reviewed more than 50 years of data (randomized, controlled; prospective cohort; and nested case-control studies) from Medline, Cochrane, and Embase registries dating from 1966 to 2016. Of the 37 high-quality publications selected, there were no statistically significant differences for risk of cardiovascular disease events (e.g., heart attack, stroke, etc.) or death between groups taking calcium supplementation (with or without vitamin D, notably) compared to those receiving placebo. Furthermore, the cohort trials did not show any significant relationship between total/dietary/supplemental calcium dose ingestion and cardiovascular mortality. However, the authors did observe “highly inconsistent dose-response relationships between calcium intake and risks for total stroke or stroke mortality.” That being said, this latter finding was notably limited by a number of potential confounding factors that largely involved imprecise measures of calcium exposure, particularly regarding “very high” calcium intake that went beyond the upper limits of recommended intake. In short, from an overall cardiovascular perspective, it appears that calcium intake is not a significant player in terms of harm to the cardiovascular system, but when looking specifically at stroke the picture is less clear at both high and low levels of calcium intake. Specifically, two studies showed that dietary calcium intake > 1,000 mg per day was associated with an increase in stroke in both men and women (relative risk [RR], 1.09; 95% confidence interval [CI], 0.99-1.21 for men; and RR, 1.13; CI, 1.02-1.26 for women). However, the authors concluded that, overall, risk estimates, even if statistically significant, were small (\pm 10% RR) and were not considered clinically significant. Of note, none of the three cohort studies

(two in Asia and one in Finland) showed any significant associations between dietary calcium intake and risk for stroke in men or women.

One exception from a more recent small Swedish study found an association of dementia among elderly women with previous history of stroke who regularly consumed supplemental calcium. In this study, 98 women with history of stroke were treated with daily calcium supplementation compared to 602 women with stroke history who were not given calcium. Those treated with calcium (1,000 mg per day) were at increased risk of developing dementia (mixed and vascular type), with an odds ratio of 2.10 and a confidence interval 1.01-4.37. Since calcium plays a central role in cell death by activating proteases that degrade critical proteins that maintain cell membrane integrity and function, the study authors hypothesized that calcium supplementation may potentiate adverse changes in vessel cell membranes that accelerate atherosclerosis and its end result of ischemia and hypotension seen in stroke and myocardial infarction.¹⁰

Ultimately, the review by Chung et al offered two significant insights: 1) To date, there are no data on the health effect of very high calcium intake levels (> 2,500 mg per day); and 2) Given the conflicting conclusions from several meta-analyses on calcium (which have contributed to confusion among healthcare providers and patients in determining what form and how much calcium to take on a daily basis), the authors recommended that all published data be made publicly available for future meta-analyses and reviews.⁹

Interestingly, whether calcium supplementation (with or without vitamin D) is beneficial or detrimental to vascular health still is not known definitively. In recognition of the absence of information, the National Osteoporosis Foundation and the American Society for Preventive Cardiology convened an expert panel to evaluate the effects of dietary (and supplemental) calcium on cardiovascular disease based on currently available research. As a result, this panel found that there is moderate-quality (level B) evidence that calcium with or without vitamin D intake from food or supplements ultimately has no relationship — positive or negative — to the risk for cardiovascular disease among generally healthy adults.¹¹ In light of this, the National Academy of Medicine has established the tolerable upper limit of intake of 2,000-2,500 mg per day as safe from a cardiovascular standpoint at this time, noting the need for further research.

CALCIUM, THE SUPPLEMENT

The big question is what forms of calcium are best? In an ideal world, calcium obtained through good nutrition and food would be sufficient for most healthy people. According to the National Institutes of Health's resource

on osteoporosis, nearly all forms of calcium supplements are absorbed relatively equally as long as it is taken with food at ≤ 500 mg at different times of the day.¹²

Furthermore, there are several different kinds of calcium available in calcium supplements. Each type contains different amounts of mineralized or elemental calcium (the essential part). Calcium orotate has a reputation for being the highest quality calcium given its easy absorption, but it may not be the most practical, cost-effective, or easily available for most people and ultimately doesn't appear to matter in terms of long-term outcomes. Other more commonly available and practical calcium supplements include the following:¹³

- Calcium orotate (90% elemental calcium)
- Calcium carbonate (40% elemental calcium)
- Calcium citrate (21% elemental calcium)
- Calcium lactate (13% elemental calcium)
- Calcium gluconate (9% elemental calcium)

How much actual daily calcium a person requires depends on age, gender, and health status. As mentioned earlier, upper recommended daily limits have been established based on current (although incomplete) research. (See Table 1.)

CALCIUM AND THE DIET

Similar to vitamins and essential amino acids and fatty acids, the body doesn't produce calcium, which must be obtained through the diet. The first step for addressing adequate calcium intake is to make sure that vitamin D levels are adequate. Vitamin D has a complex metabolic journey in the body, with important enzymatic steps in the liver, kidneys, skin, and gut. Calcium requires vitamin D for proper absorption in the brush border cells of the small intestine by upregulating transcription/translation of cellular proteins that bind, carry, and transfer calcium. Without it (or in low/insufficient levels < 20 ng/mL), calcium absorption is inhibited. At levels of 40-80 ng/mL, vitamin D is considered "sufficient" and is the target range for most people, according to the Vitamin D Council, the Endocrine Society, and the Institute of Medicine, among others.¹⁴

Dairy has long been the preferred and recommended source of calcium for most people, but the reality is that dairy is greatly lacking in most American diets. Calcium-deficient groups can include people who eat a vegetarian/vegan diet, people with gut absorption problems (lactose intolerance, celiac disease, short bowel syndrome, inflammatory bowel disease, etc.), postmenopausal women, and various other chronic diseases. However, the first step to adequate calcium intake always starts with a generally well-balanced diet that includes calcium-rich foods. Examples include oatmeal (and other whole grains), sardines, salmon, soybeans (and other beans/legumes), nuts/seeds, fortified orange juice, broccoli

Table 1: Recommended Dietary Allowance (RDA) of Calcium for Adults

Men	Daily RDA	Daily upper limit
19-50 years	1,000 mg	2,500 mg
51-70 years	1,000 mg	2,500 mg
71 and older	1,200 mg	2,000 mg
Women	Daily RDA	Daily upper limit
19-50 years	1,000 mg	2,500 mg
51 and older	1,200 mg	2,000 mg

Source: Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010

(and other dark leafy greens), and fortified rice/almond/coconut/soy milk. ■

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SPIRITUALITY

ABSTRACT & COMMENTARY

Suicide and Religious Service Attendance

By *Ellen Feldman, MD*

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

SYNOPSIS: Women who report regular attendance at religious services have a lower suicide rate than those who report not attending services at all.

SOURCE: VanderWeele TJ, Li S, Tsai AC, Kawachi I. Association between religious service attendance and lower suicide rates among US women. *JAMA Psychiatry* 2016;73:845-851. doi:10.1001/jamapsychiatry.2016.1243.

The role of spirituality and religion in medicine, and particularly in mental health, has been debated for more than 100 years. Studies in these areas tend to be difficult to interpret because of methodological limitations. Providers are left without clear answers or guidelines for best patient care, despite suggestive evidence that addressing spiritual practices and incorporating a patient's beliefs into medical treatment are an essential part of healing.¹

Multiple studies and medical investigations have compared religion and suicide rates. VanderWeele et al referred to sociologist Emile Durkheim as one of the earliest known researchers to investigate this association. In his work *Suicide*, Durkheim noted that suicide rates in Europe were higher in Protestant than in Catholic regions; he attributed the lower suicide rates of the Catholics to a number of factors, including religious prohibitions and less encouragement of autonomy (Durkheim 1897, as cited by VanderWeele).

In recent years, more studies, including some case-control studies, have examined survey data regarding suicide and religion. Few investigations contain rigid methodological criteria and even fewer have a large number of participants. Additionally, prospective, cohort designs are lacking. In other words, there are fewer studies looking forward to establish a link between risk factors and disease rather than looking retrospectively to study those who have developed a disease.

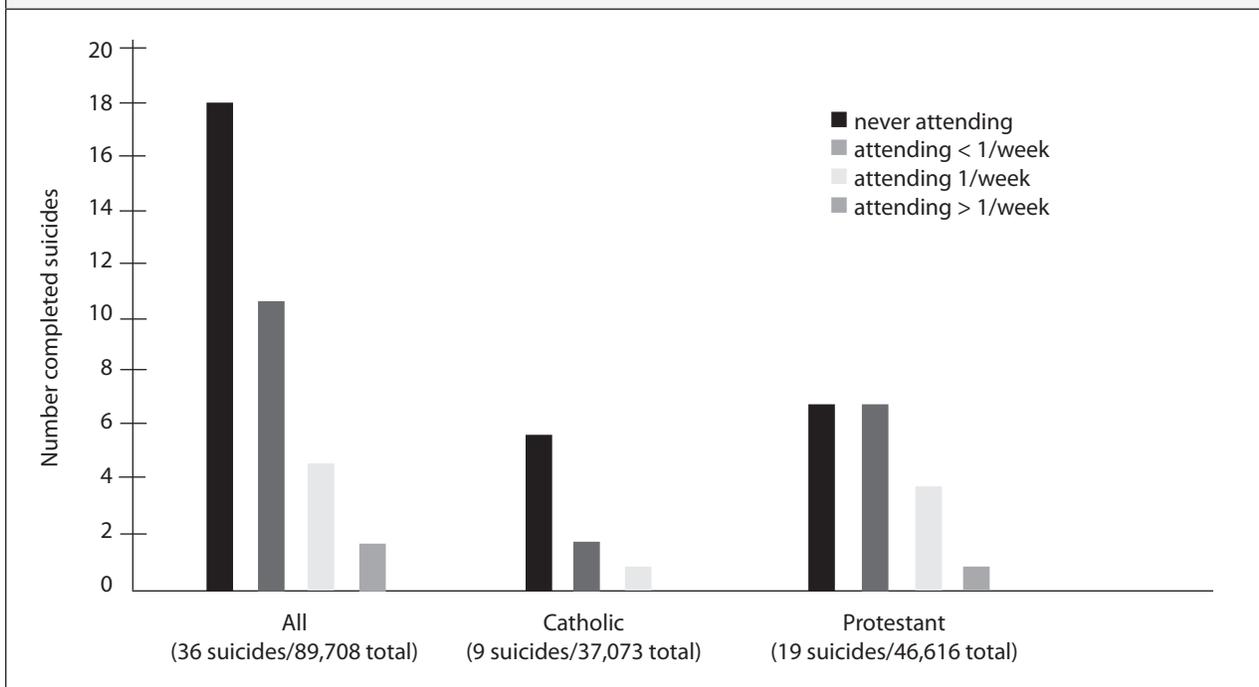
The VanderWeele et al study was designed to overcome these classical methodological challenges. Using selected data from the Nurses' Health study,² a large prospective cohort study, the investigators were able to access a large pool of participants and follow them for a significant period of time. Using specific statistical techniques, they

Summary Points

- Data from the Nurses' Health Study involving 89,708 women (ages 30-55 years) were examined to understand the relationship between religious service attendance and suicide.
- The study was both longitudinal and prospective from 1996-2010, with baseline service attendance recorded and outcome data controlled for other relevant factors such as social integration, depressive symptoms, medical conditions, and lifestyle.
- An approximate five-fold lower rate of suicide was seen in participants who reported service attendance once or more weekly compared to those who never or rarely attended.
- Results were more robust for Catholics than for Protestants.

were able to control for multiple confounding factors. The Nurses' Health Study began in 1976 and included more than 100,000 U.S. nurses between the ages of 33 and 55 years.² Participants completed a questionnaire regarding lifestyle and medical history every two years. VanderWeele et al studied the subgroup of 89,708 participants who responded to the 1996 questionnaire and included the section on religious service attendance (those who did not respond to this section were excluded from the study group). Follow-up data for suicide were collected until one of the following conditions was met: 1) completed suicide, 2) loss to follow-up, or 3) the end of the study (June 2010). In this manner, 36 suicides were

Figure 1: Number Suicides/Group Recorded by Frequency of Religious Service Attendance



identified among all the participants in this subgroup. The group was about 97% white and primarily Christian, with approximately 40% of the identified study population self-reporting as Catholic and just over 50% self-reporting as Protestant.

VanderWeele et al used results from the 1996 questionnaire about religious attendance as the primary variable in their study. Response categories regarding frequency of religious service attendance allowed a range of answers from never, to almost never to monthly, weekly or more than once weekly. Religious service attendance was included in the questionnaires only every four years. VanderWeele et al incorporated the 1992 data on lifestyle factors including religious attendance to avoid reverse causation and to include as one of several confounding factors. These researchers believed it was important to identify many prospective confounders. In order to do so, they analyzed study results in several ways, including excluding women with depressive symptoms, those taking antidepressants, and those with a history of cardiovascular disease or cancer, and adjusting the social integration score to exclude religious attendance. In all cases, the lower rate of suicide among women who attended religious services once or more weekly remained significant.

Figure 1 displays selected results showing the number of suicides in each response category. Note the number of suicides in each group is inversely related to frequency of service attendance, and this relationship appears more significant for Catholic group members.

Statistical analysis (as explained by VanderWeele et al) reveals an approximate five-fold smaller risk for suicide among those who reported attending services more than once weekly, and an even more significant seven-fold smaller risk for suicide for Catholics who reported attending services more than once weekly.

Table 1 shows these same results by incident rate per 100,000 person-years. As a comparison, the CDC reports the suicide incidence per 100,000 people increased 24% between 1999 and 2014 — from 10.5/100,000 in 1999 to 13/100,000 in 2014 (with the rate of increase greatest after 2006).³

■ COMMENTARY

VanderWeele et al set out to examine the association between suicide and religious service attendance. Recognizing the difficulty of attributing causation to a single factor, the goal was to proceed in a methodical, scientifically rigorous manner, controlling for as many confounding variables as possible and using large numbers of participants in a long-term, prospective approach. Use of the Nurses' Health study data certainly helped fulfill the criteria, giving them access to large numbers of participants over a number of years, but less desirably, it also resulted in a study of a homogenous population of largely white Christian female nurses. The findings then must be interpreted in the context of the population; there is no indication from these results that religious service attendance in general is associated with lower suicide rate. In fact, there is every indication from the relatively low suicide rate (about half that of the general population) that this is a unique group not

Table 1: Suicide Rate/100,000 Person-years for the Entire Group According to Frequency of Religious Service Attendance and Per Each Religious Group Identified

Religious service attendance 1996	All 36 suicides = incidence rate 3/100,000 person- years	Catholic 9 suicides = incident rate 2/100,000 person-years	Protestant 19 suicides = 3/100,000 person-years
Service attendance = never	7	6	3
Service attendance < 1/week	6	3	5
Service attendance 1/week	1	0.3	2
Service attendance > 1/week	1	0	1

representative of a cross-section of the U.S. population.³ Additionally, despite convincing statistical analysis showing the significance of the findings, the authors acknowledged that the low number of total suicides (36 in all) makes conclusions difficult to generalize. It will be important to find other large more diverse groups to study in a prospective fashion before applying any conclusions to population as a whole. Of equal importance is to verify the accuracy of suicide events, as this study depended on reports from next of kin and state mortality files, making it possible that unreported suicides shifted accuracy of results and statistical analysis.

The manner of selection of study participants as well as the lack of a dedicated control group are two additional factors to consider when thinking about clinical application. Respondents to the 1996 survey who did not complete the section on religious attendance were eliminated from the participant group at the onset of the study, leaving the researchers with a selected pool of respondents who had completed survey questions regarding religion. The significance of this is speculative given the lack of any further information regarding the eliminated population, but possible selection bias leaves questions about the relevance of applying these findings when working with a diverse community of patients.

Despite all of this, the popular press took an almost immediate interest in these findings with headlines in publications such as *Science Daily* to the *LA Times* stressing the “news” that religious service attendance lowers the rate of suicide among women.^{4,5} Although some articles stressed the preliminary and narrow scope of these conclusions, others tended to broaden and extend the conclusions to religious service attendance in general.

Ironically, little attention was given to another area of perhaps more controversial emerging study regarding the association between religious service attendance and martyrdom or suicide attacks. Studies in this area are quite preliminary in nature, but suggest that rituals of religion and perhaps attendance at religious services have an association with suicide in the form of an attack

or with suicide as a martyr in a range of faith-based communities.⁶

Other investigations looking at non-western religions and the eastern world have found less convincing evidence of a link between religious attendance and reduction in suicide rate, making it difficult to generalize findings from any of these studies.⁷

The results from this study revealed an association of religious service attendance with decreased suicide rate, but there is no evidence regarding cause and effect or “mechanism of action.” It may be that the effect of religion and service attendance on mental health in general is highly individualized and based on numerous interlocking psychosocial and environmental factors; future studies are needed before any conclusions can be made.

However, it is clear that this study provided specific evidence that self-reported religious service attendance is associated with a lower suicide rate in Catholic white female nurses and to a lesser extent in Protestant white female nurses. It is not too much of a stretch to postulate these findings may apply to larger group of educated white non-nurses of many religious backgrounds as well, although this should be verified independently to be sure. The question of how to use these somewhat narrow findings in clinical practice remains.

Perhaps the most important and relevant take-home message from this study is the importance of obtaining a spiritual history when working with patients. Using religion and service attendance in support of mental health of a patient best starts with understanding the role of faith in the everyday life of the patient. Opening the door to explore faith, religious beliefs, and religious community may allow a new approach to mental health and to suicide prevention in specific patients. As more studies in more diverse populations are completed, the relevance of understanding and incorporating spiritual beliefs into an individualized treatment or wellness plan will almost certainly grow and become an accepted and essential element of a medical history. ■

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CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Chocolate Consumption and MI Risk

By *Rebecca L. Fahey, MD, PhD, MBA*

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

SYNOPSIS: A prospective cohort study and confirmatory meta-analysis on Swedish adults determined chocolate consumption is associated with lower risk of myocardial infarction and coronary artery disease.

SOURCE: Larsson SC, Akesson A, Gigante B, Wolk A. Chocolate consumption and risk of myocardial infarction: A prospective study and meta-analysis. *Heart* 2016;102:1017-1022.

We are observing a trend in the medical literature on food as medicine. For instance, chocolate and cocoa flavanol consumption have demonstrated improvements in the cardiovascular health of adults.¹⁻⁶ Increasing evidence from randomized, controlled trials suggests favorable effects of cocoa on insulin sensitivity, high-density lipoprotein levels, blood pressure, and endothelial function. In addition, several prospective studies and meta-analyses have confirmed and expanded on these data. For example, the incidence of myocardial infarction (MI) was studied in relationship to chocolate consumption to clarify the assumption that chocolate has an inverse effect on coronary artery disease (CAD).

Larsson et al performed a prospective study and a confirming meta-analysis to identify patterns of MI risk among study participants. Data from two prospective cohorts, the Cohort of Swedish Men and the Swedish Mammography Cohort, included 67,640 participants after exclusions (36,535 men and 31,105 women) between 45-83 years of age. The authors used a food frequency questionnaire (FFQ) applied in 1997 as a baseline. Participants were placed into four of the eight groups based on their chocolate consumption. Covariates and demographics of the participants were obtained from a self-administered questionnaire, the Swedish National Diabetes Register, and the Swedish National Patient Register. MI case ascertainment was determined from the Swedish National Patient Register, the Swedish Cause of Death Register, and the National Board of Health and Welfare.

Summary Point

- Mounting evidence in the literature indicates that high consumption of chocolate is associated with a 10% lower risk of myocardial infarction and coronary artery disease.

Statistical analysis for all participants was based on the time range from Jan. 1, 1998, until one of three dates was confirmed: date of diagnosis of MI, date of death, or Dec. 31, 2010. Hazard ratios (HR) for covariates were established using the Cox proportional hazards regression model and established as relative risks (RR) with 95% confidence interval (CI) of MI, according to categories of chocolate consumption. The following four groups were used for chocolate consumption: never, 1-3 times/month, 1-2 times/week, and 3-4 times/week. Two multivariate models were established to categorize the covariates, and the first model was formed into groups by age and sex. The first multivariate model included the following covariates: education, family history of MI before age 60, smoking, aspirin use, walking/bicycling, exercise, total energy intake, processed meat, fruits, and vegetables. The second multivariate model included the above covariates plus body mass index (BMI), history and diagnosis of diabetes, hypertension, and hypercholesterolemia at baseline. The HR was established as satisfactory using Schoenfeld residuals.

Within the Cox model, a continuous variable for the median value of chocolate consumption within groups was established to determine linear trends. This variable was used to examine the association between MI risk and chocolate consumption and was modified by sex, education, and a history of diabetes, hypertension, and hypercholesterolemia at baseline. The likelihood ratio test was used to verify the statistical significance of effect.

A meta-analysis was performed combining the results of the Swedish study with previous prospective studies on chocolate consumption and MI or CAD risk. An established level of chocolate consumption was assumed to be 30 grams.

The Swedish study, which lasted a mean of 13 years with 67,640 participants found 4,417 cases with 897 deaths from MI. Interestingly, those individuals who consumed the most chocolate (≥ 3 -4 servings/week) were more likely to have a college education, have higher total energy intake, and eat more processed meat, and were less likely to smoke, be overweight, and have a history of diabetes, hypertension, and hypercholesterolemia. The study found that chocolate consumption was associated with a lower MI risk even with the covariates mentioned above. In the first multivariate model, men and women who consumed the most chocolate (≥ 3 -4 servings/week) had a 20% (95% CI, 10-30%; $P < 0.002$) lower risk of MI than non-consumers of chocolate. In the second multivariate group that was adjusted for BMI and a history of diabetes, hypertension, and hypercholesterolemia at baseline, the reduction in MI risk was 13% (95% CI, 2-23%; $P < 0.04$).

The results of the five prospective studies and the Swedish study selected for the meta-analysis found 6,851 CAD cases from 144,823 adult participants. The data from these prospective studies came from five different countries (Sweden, Germany, United Kingdom, United States, and Australia). When results from all six studies were joined, the overall RR for the highest vs. lowest category of chocolate consumption was 0.90 (95% CI, 0.82-0.97), with little heterogeneity ($I^2 = 24.3\%$) between studies. The dose-response meta-analysis overall RR per 50 g/week of chocolate consumption was 0.95 (95% CI, 0.92-0.98) without heterogeneity between studies ($I^2 = 0\%$). Two of the six studies identified the type of chocolate consumed: chocolate bars, plain chocolate, chocolate snack bars, and plain cocoa for drinks.

■ COMMENTARY

Increasing evidence from randomized, controlled trials and prospective cohort studies emphasizes the benefits of regular chocolate consumption.¹⁻⁸ Participants consumed different types of chocolate during the studies, and the authors did not distinguish between dark and milk chocolate. A lower risk of MI and CAD is assumed to

be stronger for dark chocolate, which has higher cocoa content than milk chocolate. Further studies are needed to clarify the amount and types of chocolate. Chocolate has been proven to affect insulin sensitivity, vascular endothelial function, and activation of nitric oxide, and has been shown to decrease oxidation, blood pressure, inflammation, plaque formation in the vasculature, and formation of blood clots.^{6,9,10} Its beneficial properties come from the polyphenols and flavonoids (flavan-3-ol, epicatechin).¹¹ Polyphenols are abundant micronutrients found in plants that have antioxidant properties. Flavonoids are a specific polyphenol found in chocolate, vegetables, fruits, legumes, red wine, and green tea.^{9,11}

Overall, there is a strong association between chocolate consumption and decreased risk for cardiovascular disease.¹⁻⁶ Along with a healthy diet, the consumption of high (> 70%) cocoa solid (flavanol)-containing chocolate bars is recommended to decrease a 10-year risk of cardiovascular disease.³ Causality has been established between intake of flavanols and improved endothelial function.¹² More research is recommended on the benefits of milk vs. dark chocolate and the dose-response relationship and the effects on cardiovascular disease risk. One major limitation of this study was that the FFQ had only one question on chocolate consumption. Not all health benefits of chocolate are created equally: The darker the chocolate, the more cocoa solid it contains and the more flavanol. Although, studies have suggested that (> 70%) cocoa solids have the most overall benefits, it is hard to know actually how much cocoa solid or flavanol is available in the chocolate after processing.¹³

The overall recommendation is to increase consumption of plants containing polyphenols (flavanol) because of the antioxidant capabilities. Increased consumption should include chocolate, vegetables, fruits, legumes, red wine, and green tea.¹¹ Those who consumed 30 grams (the average bar consumed by Swiss men) of chocolate (≥ 3 -4 servings/week) decreased the risk of CAD the most. Consuming dark chocolate (> 70% cocoa solids) would increase the amount of flavanols in the diet. ■

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DIETARY SUPPLEMENTS

ABSTRACT & COMMENTARY

Supplements Instead of Food? A Specific Case for Yes

By David Kiefer, MD, Editor

SYNOPSIS: A nutritional supplement helped malnourished nursing home residents gain weight and improve quality of life, more so than dietary advice and counseling.

SOURCE: Parsons EL, Stratton RJ, Cawood AL, et al. Oral nutritional supplements in a randomised trial are more effective than dietary advice at improving quality of life in malnourished care home residents. *Clin Nutr* 2016; Jan 11. pii: S0261-5614(16)00003-0. [Epub ahead of print].

This study compared oral nutritional supplements (ONS) with dietary advice in a malnourished institutionalized population with respect to quality of life (QL; the primary outcome) and nutritional intake (the secondary outcome). The U.K. study was undertaken to address the problem of malnutrition in nursing homes. A total of 104 residents of said facilities were recruited and randomized to ONS or dietary advice provided by a dietitian for 12 weeks.

The researchers started by searching for all nursing/care homes in Hampshire, England (n = 633), and excluded facilities owned locally or by the National Health Service, those with less than 10 beds or for people younger than 50 years of age, and those just for advanced dementia, drug dependency, and learning disabilities; the authors did not note the reason for these exclusions. All told, 53 homes participated, and the focus was on adults ≥ 50 years of age who were at medium or high risk for malnutrition based on the MUST scale. (See Table 1.) A total of 1,455 residents were screened, 598 of whom met adequate MUST criteria (score ≥ 1), although only 132 passed a variety of exclusion criteria (outlined in detail in the article). Of the 132, only 104 gave informed consent for participation in the procedure.

The 104 residents selected for the trial were then randomized to ONS or dietary advice. For the ONS group, residents were able to select a variety of ONS depending on personal preference, but all provided 600

Summary Points

- The authors randomized 104 people (average age 88 years) in nursing homes to receive either nutritional supplementation (target 600 calories and 16 g of protein) or dietary advice for 12 weeks.
- The nutritional supplementation group had 6-8% greater quality of life by standardized measures than the dietary advice group, and gained 1.2 kg (vs. 0.5 kg) during the study period.

kilocalories (kcal) and 16 grams of protein. Examples of ONS chosen by residents include drinks, puddings, and soups, and they also varied by flavor, volume, and energy density; most residents chose a fortified drink providing 1.5-2.4 kcal/mL. Those residents in the dietary advice group received written information requesting that they focus on eating foods and drinks of “high energy.” This written information was reviewed, in person, with a dietitian at baseline and week 6.

Measurements were taken at baseline, six weeks, and 12 weeks, and included MUST criteria, body weight, height, BMI, and QL (using EuroQol that measures mobility, self-care, usual activities, pain, anxiety; and EuroQol visual analog scale [VAS], ranging 0-100, a

Table 1: Malnutrition Universal Screening Tool (MUST) Criteria

- Body mass index (BMI): > 20 kg/m² = 0 score, 18.5-20 kg/m² = 1, < 18.5 kg/m² = 2
- Unplanned weight loss in past 3-6 months: < 5% = 0 score, 5-10% = 1, > 10% = 2
- Acute illness and no nutritional intake for more than five days: score 2
- Low risk if score 0, medium risk if score 1, high risk if score 2 or more

self-assessment). (See Table 1.) Both the EuroQol and the VAS were adjusted to “incorporate judgments made by representative samples of the general population,” essentially a referenced calculation allowing ranges of -0.059 to 1.0 and -0.073 to 1.0, respectively. In addition, a 24-hour dietary recall was used to estimate energy and macronutrient intake, and residents were asked to verbally respond to a series of questions pertaining to hunger and satiation.

An intention-to-treat analysis of the 104 study subjects was undertaken on the ONS (n = 53) and dietary advice (n = 51) groups. The average age was 88.5 years, and 86% were female. Per MUST, 46% were medium risk and 54% were high risk. Baseline characteristics were similar, except for an eight-point higher VAS score in the ONS group. Thirty-four residents did not complete the study (most commonly due to “confusion” secondary to “ill health”), 14 in the ONS group and 20 in the dietary advice group. There was no significant demographic differences between these groups, nor with those residents who completed the study.

Results are displayed in Table 2. After 12 weeks, the ONS group showed statistically significant improvements in QL, both in the EuroQol calculation and VAS (P values 0.005 and 0.006, respectively). For both of these parameters, when the measurements were averaged over the 12-week period to estimate an average QL for that period, the ONS group was again statistically higher: for EuroQol, 0.489 for ONS vs. 0.449 for dietary advice (P = 0.013), and for VAS, 0.531 for ONS vs. 0.507 for dietary advice (P = 0.015). The researchers reported some of these findings as a percentage improvement to make the numbers more clinically relevant. (See Table 2.)

Other results included a significant increase in body weight in the ONS group over the 12 weeks (1.22 kg; P = 0.010) vs. an insignificant increase in the dietary advice group (0.48 kg; P > 0.05). An extremely detailed breakdown of micro- and macro-nutrient intake revealed that the ONS group consumed 351 kcal of calories and 12.2 grams of protein more than the dietary advice group per day. Obviously, most of this amount was due to the ONS ingestion, although higher voluntary food intake in the ONS group also accounted for some of this. The

ONS also tipped the scales in favor of higher intake of “... most other nutrients ...” as detailed in article.

■ COMMENTARY

In the midst of the discussion of food over supplements, à la Michael Pollan, it was difficult to stomach (pun intended) the results of this study. Isn't it always better to consume whole foods, organically grown if possible, to provide nutrition and prevent illness? The researchers of this study looked at just this question in a very select group of people: those who were malnourished, elderly, and institutionalized. They found that dietary advice and two meetings with a dietitian couldn't compete with ONS of a variety of formulations with respect to QL, weight gain, and nutrient intake. Even though the target calorie supplementation wasn't reached, the residents displayed significant benefit over the study period.

Obviously, this demographic isn't relevant to all clinical practices. But the results for this obscure subgroup of people nonetheless possibly could be extrapolated to other populations who may have marginal nutrition. And ONS is not that uncommon of a nutritional approach when we think of how many of our patients (and selves, friends, families) turn to protein shakes, smoothies, and juices to take the place of skipped meals or fortify one's nutrition during extremes of activity, stress, work, etc.

What should we tell patients based on this study? Certainly, an individualized decision, although one approach might be to follow the methodology of this study and use the MUST criteria. For example, the MUST criteria would whittle down significantly who might truly benefit from ONS; a 0 on the MUST scale may dissuade the use of ONS to achieve nutritional goals, whereas those patients at medium and high risk (scores 1+) should seriously consider ONS to boost QL and weight. There are few reasons not to jump on the ONS bandwagon other than cost (not mentioned in the trial) and logistics (extra staff involvement to prepare and distribute the ONS). There was some inkling from this study that a boost of nutrition from ONS might even nudge voluntary food intake — a nice side benefit, and

Table 2: Study Results for the Oral Nutritional Supplements and Dietary Advice Groups

Variable	Oral Nutritional Supplements	Dietary Advice
Quality of life, as per EuroQol	0.496 (8.3%)*	0.364
Quality of life, as per VAS	0.535 (7.3%)*	0.457
Body weight change (kilograms)	+ 1.22	+0.48

* Percentage that the ONS scores were above the dietary advice scores; this percentage represents “...a proportion of the entire range of possible scores.”

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one that the food > supplements advocates certainly could support.

Before we pass out smoothies to all our malnourished patients, a few comments on the study itself may prompt some reflection. There were some unknowns about the true ONS intake in the intervention group; the ONS was just a target amount, but residents remained in the study regardless of true intake. It is difficult to say whether true intake of ONS would have been more or less than the estimates, clearly affecting study results. Also, the control group, dietary advice, may not have had a fighting chance. Other dietary intervention studies often include weekly dietitian visits, so with only two visits over 12 weeks, it could be argued that the residents would be unlikely to incorporate such dietary suggestions into their lives. Furthermore, it would be interesting to note what might happen with a true control group, either one with no intervention or one with a nutritional supplement that provided little to no supplemental nutrition. Ideally, these control interventions, in addition to

being randomized, would be blinded — a difficulty with dietary intervention studies, but nonetheless an approach that would enhance the believability of the results. The age of the study population (average 88.5 years) also at least gives one pause about the relevance of a dietary advice arm based on written information, supplemented only twice with a dietitian consult. Perhaps the significant percentage of dropouts (in each arm) speaks to the onerous aspect of the intervention attempted in this population, if not simply because of the complicated health histories in this demographic.

Despite these criticisms, this was a gallant effort to reach a deserving population with one of life's basic needs, healthy nutrients, and demonstrate what we all know, that adequate nutrition certainly correlates with improved quality of life. And the demonstrated improvements (7-8%) with ONS compared to dietary advice may even be on par with other medical and non-medical interventions in this population. ■

CME QUESTIONS

- Which of the following statements about calcium is false?**
 - Calcium intake is ideally obtained through a well-balanced healthy diet, with use of supplements to ensure at least 1,000 mg/day.
 - Calcium is essential for proper functioning of various systems in the body at a cellular level.
 - Calcium causes cardiovascular disease and supplementation should be avoided.
 - Vitamin D is essential for adequate calcium absorption in the gut.
- According to VanderWeele et al, which of the following can providers confidently recommend to patients?**
 - Increase religious service attendance to decrease risk of suicide.
 - Exploring a spiritual history and incorporating elements of faith into a treatment plan may help with mental health.
 - There is no clear or suggestive evidence that religious service attendance affects mental health or suicide rate.
 - Attending religious services monthly can assist in decreasing suicide rates in most adult patients.
- Which of the following antioxidants has been shown to decrease the risk of cardiovascular disease?**
 - Vitamin C
 - Vitamin A
 - Flavanol
 - Vitamin D
- Parsons et al found that oral nutritional supplementation in a malnourished, elderly, institutionalized population over 12 weeks led to which of the following?**
 - Improved quality of life by VAS, but comparable to the dietary advice group
 - A non-significant trend toward weight loss over the 12 weeks
 - Improved quality of life by both EuroQol and VAS, statistically significantly more than what was seen in the dietary advice group
 - An intake of 1,200 kcal more daily than the baseline diet

[IN FUTURE ISSUES]

Omega-3 fatty acids
and dietary retinopathy

Cranberries
for prevention
of urinary tract infections

Mind-body therapies
for neurofibromatosis

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in pediatrics

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