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OBESITY

ABSTRACT & COMMENTARY

Popular Diets for Weight Loss

By Dónal P. O'Mathúna, PhD, and Catrina Feeney

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing and Human Sciences, Dublin City University, Ireland; and Ms. Feeney is a Student Dietician, The Ohio State University, Columbus, Ohio

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

With the beginning of another year, many will be resolving to lose some weight. According to consumer surveys conducted for industries manufacturing low-calorie foods and beverages, 54% of Americans were trying to lose weight in 2010, up from 33% in 2004 and 24% in 2000.¹ The U.S. market for all weight loss products and services is now worth \$60.9 billion.²

This article will examine some of the popular diets currently being promoted. A future article will examine diets to be reviewed in a soon-to-be-released *Consumer Reports* article. Space does not permit a review of all commonly used diets, so only a few popular ones will be selected. Other diets have been reviewed here more recently, including high-protein, low-carbohydrate diets³ and the human chorionic gonadotropin (HCG) diet.⁴ The diets examined here illustrate the variety of strategies being advocated, and the varying degrees to which these are based on healthy nutrition principles. Different organizations warn against diets promoted

on the basis of certain traits, some of which have been compiled in Table 1.

Weight loss programs based on inaccurate principles rarely achieve successful weight loss, especially in the longer term. This leads people to either attempt other ineffective programs or become defeated and gain more weight. Harm can also occur if a diet encourages nutritionally unsound practices, leads to too rapid weight loss, or leads to the neglect of essential nutrients. Given how many Americans are currently trying to lose weight, and how important this is for health, health care professionals should be able to help patients evaluate popular diets and identify those based on the best available evidence.

ALKALINE DIET

The alkaline diet is primarily a plant-based diet. Fresh vegetables and fruit are prioritized, along with foods that produce more alkaline urine. Dairy products, meats, eggs, and some nuts produce more acidic urine and are discouraged, as are more processed

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Table 1. Warning Signs in the Promotional Materials for Popular Diets

- Make claims that, according to available scientific evidence or generally recognized recommendations, are too good to be true.
- Label specific foods or food groups as “good” or “bad.”
- Require a certain vitamin, mineral, or commercial product as the key to success.
- Eliminate an entire food group (like carbohydrates or dairy).
- Promise quick and easy weight loss without much effort.
- Guarantee that everyone can lose specific numbers of pounds within a certain time (like 10 pounds in 10 days).
- Recommend consuming less than 1000 calories a day.
- Fail to mention the importance of physical activity or exercise.
- Provide testimonials more than scientific evidence for effectiveness.

foods, white flour, white sugar, and caffeine. Some promoters of the alkaline diet claim that it lowers the blood pH that overcomes unhealthy acidity in the body. This is said to lead to weight loss, and treatment of arthritis, diabetes, and cancer.

Scientific Evaluation. Different tissues in the body have different pH values (ranging from 1.3-3.5 in the stomach to 8.8 in pancreatic fluid).⁵ The pH of urine varies between 4.6 and 8.0, and this is influenced by diet. More alkaline foods can reduce the risk of kidney stones, but the only relevant article found in PubMed identified no evidence to support the claims made for the alkaline diet other than those due to increased consumption of plant foods.⁵ This review did not address the alkaline diet's effectiveness regarding weight loss.

Concerns and Recommendations. The alkaline diet has beneficial aspects, particularly in promoting consumption of fruits and vegetables. If these replace other high-calorie foods, weight loss may result. However, this has nothing to do with changing the body's pH. The alkaline diet can lead to insufficient protein due to meat restrictions, and insufficient calcium, due to dairy restrictions. People on the alkaline diet should ensure they obtain sufficient essential nutrients.

GRAPEFRUIT DIET

Grapefruit first appeared in fad diets in the 1930s Hollywood Diet, a forerunner of the unofficial Mayo Clinic Diet. This recommended eating grapefruit before

every meal for 12 days, and restricted total consumption to 800-1000 calories daily.⁶ The claim is made that grapefruit stimulates enzymes in the body that metabolize fat. The diet has many variations, but a similar pattern of fresh grapefruit before meals of primarily low-calorie foods. Promises of losing 10 pounds in 12 days are commonplace.

Scientific Evaluation. Grapefruit has been the subject of some research encouraged by the citrus growing industry. Several compounds have been isolated and shown to have beneficial cardiovascular effects in animals.⁶ A few human trials have produced conflicting results, with these effects continuing to be investigated.

For weight loss, a few clinical trials have been published recently. Ninety-one obese patients were randomized to either half a grapefruit, grapefruit juice, grapefruit extract capsules, or an equivalent placebo taken three times daily before meals.⁷ Over 12 weeks, the fresh grapefruit group lost 1.6 kg, the grapefruit juice group lost 1.5 kg, the grapefruit capsule group lost 1.1 kg, and the placebo group lost 0.3 kg. The differences were significant ($P < 0.05$). In another trial, 85 obese adults were randomized to consume 127 g of either fresh grapefruit, grapefruit juice, or water before three daily meals (called a preload).⁸ Individual daily energy expenditure was calculated and meals planned to provide 12.5% fewer calories than expended. For the first 2 weeks, everyone followed only the restricted calorie diet, and for the next 10 weeks they followed the diet plus the different

Summary Points

- Many different approaches to dieting are popular, with varying reliability in the recommendations given.
- The widespread promotion of popular diets highlights the importance of education about well-established dietary guidelines.
- Some popular diets can be harmful by promoting poor dietary habits or neglecting important lifestyle factors.

preloads. Average weight loss of 1 kg occurred during the first 2 weeks, with this increasing by 13.3% ($P < 0.0001$) during the preload phase. Average overall weight loss was 7%. However, no significant differences in weight loss or body fat composition existed between the three groups.

The most recent study randomly assigned 74 overweight and obese adults to those who consumed half a fresh grapefruit before meals for 6 weeks or a control group.⁶ All subjects consumed their usual diet except they eliminated selected fruit and vegetables containing similar polyphenols to grapefruit. No statistically significant differences in body weight, body composition, or lipid profile were found between the two groups.

Concerns and Recommendations. Grapefruit is a nutritious food that is being shown to have some health benefits. However, the approach taken in the grapefruit diet has not been shown to be effective, except by way of restricting caloric intake. Although grapefruit is nutritious, concerns have been raised about potential drug interactions. Grapefruit can lead to elevated blood levels of statins, but a daily grapefruit or glass of grapefruit juice does not lead to clinically significant changes.⁹ Consuming large amounts of grapefruit could have more significant effects and should be avoided in those taking statins, and numerous other medications including specific antiarrhythmics, calcium channel blockers, and immunosuppressants.¹⁰

PALEO DIET

The Paleo (or Paleolithic) diet claims to be the world's healthiest diet based on the foods that our hunter-gatherer ancestors would have eaten during the Stone Age. In the last several thousand years, humans have evolved little, but our diets have changed dramatically and so have the diseases we experience.¹¹ The introduction of cereal grains, dairy products, refined sugar, and processed fats are said to have created a mismatch between our diet and our genetic adaptation. Therefore, a diet rich in lean

meat, seafood, fruits, vegetables, and nuts (the Paleo diet) will be more healthy.¹²

Scientific Evaluation. Advocates of the Paleo diet note that hunter-gatherer communities have lower incidences of degenerative diseases.¹³ Markers such as blood pressure, insulin sensitivity, body mass index, and bone health tend to be better than in those consuming typical Western diets. For example, 13 type 2 diabetes patients consumed either a Paleo diet or one based on contemporary dietary guidelines for diabetes.¹⁴ After 3 months, participants crossed over to the other diet. Significantly better improvements were found on the Paleo diet for weight loss (-3 kg; $P = 0.01$), waist circumference (-4 cm; $P = 0.02$), body mass index (-1; $P = 0.04$), and other cardiovascular markers. However, the study was terminated early due to difficulties recruiting sufficient subjects to obtain the number determined by a pre-study power calculation. About five other trials with between 9 and 29 subjects found various improvements with the Paleo diet.¹⁵ None of these lasted longer than 12 weeks.

Concerns and Recommendations. Twenty popular diets were evaluated by nutrition experts for *U.S. News & World Report*, with the Paleo diet getting the lowest ranking.¹⁶ Concerns were expressed at its high fat content (39%) due to its high protein content (39%). The diet is low in fiber, calcium, vitamin D, and iron.¹² It also increases average household food costs by about 10%.¹² The underlying evolutionary principles and dietary intakes have been critiqued as implausible and impossible to verify.¹¹ Anthropologists claim that up to 80% of hunter-gatherer diets were plant-based, with much less meat than advocated in the Paleo diet.¹⁷ The increased plant consumption in this diet is commendable.

SOUTH BEACH DIET

The South Beach diet is an adaptation of the high-protein, low-carbohydrate diet popularized as the Atkins diet.¹⁸ The goal is to eliminate “bad fats and bad carbohydrates,” which are those metabolized more quickly. The South Beach diet has three phases.¹⁹ The first lasts 2 weeks and claims rapid weight-loss of 8 to 13 pounds. It does this by severely restricting specific foods, particularly carbohydrates, sugars, dairy, and alcohol, but also fruit. Phase 2 is for sustained weight loss with an emphasis on consuming lean protein and low-fat dairy, with the gradual introduction of whole-grain carbohydrates and fruit. Phase 3 is for maintaining body weight at the level achieved. It involves expanding the range of plant foods, while promoting consistent meal times, reasonable portion sizes, healthy snacks, and water consumption. In

this stage, the South Beach diet encourages similar proportions of protein to the Atkins diet (26% and 29%, respectively), but with less fat (40% and 62%) and more carbohydrates (33% and 9%).²⁰

Scientific Evaluation. The first phase of the South Beach diet has been criticized as overly restrictive. Such approaches may result in weight loss because of how few calories they allow, but can provide less than the minimum recommended 1000 calories per day.⁷ On the other hand, the South Beach Phases 2 and 3 take advantage of the growing evidence supporting the effectiveness of high-protein, low-carbohydrate diets for weight loss over 6 months and possibly 12 months.³ The quality of Phase 2 South Beach was found to slightly exceed the recommendations of the 2005 USDA Food Guide Pyramid, while Phase 3 was slightly below.¹⁹ Evidence for the long-term effectiveness of the South Beach diet is lacking.

Concerns and Recommendations. The South Beach diet has strengths and weaknesses. A systematic evaluation of the nutrition statements in the South Beach book identified 42 different claims.¹⁸ Of these, 14 (33%) were supported by peer-reviewed articles, 7 (17%) were not supported by the literature, 18 (43%) were somewhat supported and not supported, and 3 (7%) had no relevant published papers.²¹ Peer-reviewed articles were not identified to support claims about the diet's effectiveness, nor how it allegedly leads to weight loss.

During the highly restrictive Phase 1, some people may be encouraged by rapid weight loss, but others may be deterred or defeated by its severity. This phase may lack sufficient calories and essential nutrients. Phases 2 and 3 are much more balanced and provide a structured approach to sustained weight loss and maintenance. However, concerns have been raised about the elevation of some cardiovascular risks when people adhere to high-protein, low-carbohydrate diets for extended periods.³ Further research is needed to investigate these concerns.

CONCLUSION

A common question is whether eating multiple times during the day increases metabolism and promotes weight loss.²² The answer had been “kept secret” until the 3-Hour Diet promised to take 10 pounds off in 2 weeks by controlling meal times.²³ However, 40 years of research have provided no consensus on this, other than that overall daily calorie consumption is more important than how frequently one eats during the day.²⁴

The obesity epidemic has spawned numerous diets,

making it important that patients be encouraged to identify and avoid the traits listed in Table 1. Any diet recommending fewer than 1000 calories per day should not be undertaken without medical supervision.²⁵ Evidence-based reviews of new weight loss programs are available from a number of reliable organizations. As well as being able to evaluate popular diets, health care professionals should be aware of the most recent evidence-based dietary guidelines.²⁶ In addition, researchers are starting to systematically evaluate some of the more popular diets, the results of which will help clinicians to better counsel patients about these diets.²⁷

RECOMMENDATIONS

The principles of effective weight loss are uncomplicated, even if easier said than done. The basic principle is to consume fewer calories than are used. For safe, effective, long-lasting weight loss, aim to lose 1-2 pounds per week, which requires consuming 500-1000 calories less than is used each day.²⁵ This may seem like a slow rate of progress, but gradual sustained weight loss will be easier to maintain and allow time for the necessary lifestyle changes — including gradually increased physical activity. How people reduce their calorie intake can be tailored to the individual. Some eliminate high-calorie foods, others prefer replacing certain foods with lower calorie options, some get involved in different calorie-counting programs, while others focus on increasing physical activity. The important thing is to reduce intake and increase output. ■

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RESPIRATORY INFECTIONS

Integrative Approaches for Cold and Flu

By Luke Fortney, MD

Integrative Family Medicine, Meriter Medical Group, Madison, WI

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

Every year in September throughout the United States, students return to school, and many people return to work from vacation and summer break. As weather cools with the coming fall and winter, people gather in close proximity in colleges, schools, daycares, clinics, and workplaces. Humidity drops and indoor heating leads to dry air. Many experts and laypersons alike have postulated that these and other factors contribute to the rise in acute respiratory infections (ARIs) seen across the population. Also referred to as upper respiratory infection (URI) or the common cold, these infections have considerable overlap with pharyngitis, sinusitis, otitis, bronchitis, and pneumonia. While rhinovirus is the most common agent of infection, influenza is the most dangerous in terms of morbidity and mortality.¹

Although the common cold is considered a nuisance illness, it carries considerable cost both in terms of health care dollars and overall negative impact on the economy. Data extrapolated from a United States telephone survey conducted in 2001 suggest that about 500 million non-influenza viral respiratory infections occur every year, resulting in estimated direct costs of \$17 billion and indirect costs of \$22.5 billion annually.² On average, adults experience 2.5 colds per year,³ while children experience five per year.⁴ Furthermore, while URIs are a nuisance illness, they have measurable, significant decrements

on quality of life in terms of physical, social, and emotional functioning.⁵ Accordingly, there has been increased emphasis for researchers to measure the effectiveness of novel URI treatments based on health-related quality-of-life impact.

INTEGRATIVE OPPORTUNITY

Interestingly, there exists no effective cure for ARIs, and treatment options generally have only mild-to-modest effect on symptom reduction. Some patients appear to be more prone to ARIs than others, but the reasons for this are also not completely understood. Although many investigations have failed to identify clear determinants of susceptibility, prevention, and cure, a Cochrane review found that sick-time isolation, hand washing, and use of protective masks play a significant role in preventing the spread of viral respiratory infections.⁶ In addition to these effective measures, there are other sensible approaches that can be considered for ARI management. Being able to offer patients various safe and effective treatment options helps reduce harm associated with inappropriate use of antibiotics for ARIs.⁷

Stress has long been recognized as a factor in ARI susceptibility and symptom severity. For example, university health clinics have long observed increases in ARIs among students experiencing increased stress during mid-term or final exams. Research shows

that immune function and mood are correlated, with positive affective states resulting in stronger immune function and decreased illness.⁸ In one study, employees who enrolled in a mindfulness-based stress reduction program demonstrated less anxiety and stress. They also showed significant increases in influenza vaccine titers compared to controls.⁹ In working with patients, it is always valuable to ask about increased stress and offer helpful suggestions to minimize the burden of stress when possible. Deep breathing exercises, simple mindfulness practices, and a quiet day of rest can be helpful for treating ARI symptoms.¹⁰

Tobacco use — cigarette smoking in particular — appears to prolong symptoms and increase frequency of ARIs.¹¹ Accordingly, an integrative medicine approach to treating ARIs should include a quick screening for tobacco use, particularly cigarette smoking. Smokers who present with ARIs present an ideal opportunity for cessation counseling.

Conversely, moderate alcohol intake appears to be protective against ARIs. One study found that 1-2 drinks a day, especially red wine, seems to predict fewer and less severe ARIs compared to teetotalers or heavy drinkers.¹² It is postulated that the beneficial effects of beer and wine consumption may be due to the antioxidant and anti-inflammatory effect of polyphenols. However, that the alcohol itself may have a beneficial effect on ARIs cannot be excluded.¹³

In relation to vitamin D, several randomized, controlled trials (RCTs) suggest that supplementation for the treatment or prevention of URIs may be beneficial.¹⁴ People with higher serum levels of 25-OH vitamin D seem to have greater pulmonary function as measured by FEV₁ compared to people with lower levels. This may be due to immune-modulating and antimicrobial effects of vitamin D,¹⁵ or its ability to remodel lung tissue and improve lung function.¹⁶ However, data from the VIDARIS trial, an RCT, published in the *Journal of the American Medical Association* found that vitamin D supplementation did not reduce the incidence of respiratory tract infections in adults who have sufficient serum levels of vitamin D.¹⁷ Nonetheless, for patients who are significantly low in 25-OH vitamin D serum levels (< 30 ng/mL), supplementation with cholecalciferol (vitamin D3) 1000-2000 IU should be recommended.¹⁸

Although the cure for the common cold remains elusive, many therapies can improve and possibly shorten the duration of ARIs. A systematic approach that includes choices for patients is ideal. Including patients as active participants in their own health

Summary Points

- Frequent handwashing, avoiding sick contacts, smoking cessation, limiting alcohol to low-to-moderate use, gargling salt water, ingesting honey, reducing stress, and avoiding vigorous exercise while sick are helpful in managing acute respiratory infections (ARIs).
- For patients who are deficient in 25-OH vitamin D levels, supplementing with 1000-2000 IU of cholecalciferol (vitamin D3) is recommended for prevention and treatment of ARI.
- Andrographis, elderberry, pelargonium, probiotics, and vitamin C and zinc supplementation show promise and appear to be safe when used short term for the treatment of ARIs.

care is beneficial from an integrative medicine perspective. Furthermore, research suggests that having empathetic physicians who are mindfully present and listen to patients with ARIs actually decreases both duration and intensity of symptoms, as well as improves objective measures of illness such as IL-8 and neutrophils.¹⁹ The power of placebo in the ARI setting should not be underestimated; rather, it should be viewed as stimulating the natural healing response. One ARI study found that participants who were randomized to a “no-pill” group (meaning they were not given anything in pill form) showed longer and more severe illness than those who received pills. For those participants who believed in and received pills (regardless of whether or not it was placebo), illnesses were substantively shorter and less severe. These findings support the general idea that beliefs about treatments are important and should be taken into consideration when treating patients presenting with ARIs.²⁰ It is with this background in mind that the patient encounter should be approached, with intention to stimulate the healing response through mindful presence and empathy. In this setting, the particular agents to choose from may not be as important, it turns out, as the process of choosing in the presence of a supportive and listening physician.

OTHER LIFESTYLE ADJUSTMENTS DURING ARI

With ARIs, an integrative approach should begin with hand washing and appropriate hygiene to prevent spreading the infection to others. This effect appears to be, not surprisingly, most robust among children. The highest quality RCTs suggest respiratory virus spread can be prevented by hygienic measures, particularly hand washing, especially among younger children.⁶ Hand washing is most effective if it is at least 20 seconds in duration (or humming “Happy Birthday” from beginning to end

twice). Although hand sanitizer is helpful, it is not as effective as hand washing. If used, enough volume of material should be expressed to cover all surfaces of the hands and fingers and rubbed together until dry.²¹

Although regular exercise should be encouraged for all patients, intense exercise (such as distance running) should be temporarily halted while a patient is symptomatic with ARIs. There is research showing increased risk of ARIs during excessive cardiovascular exercise.²² In general, patients should be encouraged to stay gently active, such as short walks or light home yoga as examples. Additionally, as in a hospital setting where incentive spirometry is widely used, patients should be encouraged to take slow, deep breaths every 1-2 hours while awake to prevent atelectasis and to improve pulmonary circulation.²³

Nutritionally, recommendations should include low sugar (e.g., table sugar, especially high fructose corn syrup) intake during ARIs. Sugar suppresses the immune system by inhibiting the ability of white blood cells to engulf bacteria and viruses.²⁴ Practically, this means avoiding soda, candy, sweets, and desserts. Paradoxically, honey shows promise as a remedy for ARIs. In addition to its demulcent effects, honey has antioxidant and immunomodulating properties that may explain its antimicrobial effects. Research shows that 1-2 teaspoons (5-10 mL) can significantly reduce nighttime cough frequency and severity, as well as improve sleep when compared to placebo in children ages 2 years and older with ARIs.²⁵ Honey is also at least as effective as dextromethorphan or diphenhydramine in children.²⁶ Together with chamomile, licorice, or ginger tea, honey can be a comforting remedy for ARI symptoms.²⁷ There also is evidence to support chicken soup as a remedy for ARIs,²⁸ but it is recommended to use free-range chicken stock and organic ingredients due to the overall health uncertainties in the risk associated with pesticides and other synthetic chemicals.²⁹ Hot toddies also can be considered for adults with no risk or history of alcoholism (e.g., warm tea with honey with a small amount of rum or brandy taken at night). Finally, although the simple therapy of gargling salt water has mixed data, it is safe and can be relieving for associated pharyngitis as well as helping with eustachian tube dysfunction.³⁰

SUPPLEMENT AND BOTANICAL UPDATES

There is some evidence for a handful of dietary supplements with evidence to support their use. Although the three primary species of *Echinacea purpurea* may be the most widely recognized cold remedy, recent research findings have been mixed,

especially for *Echinacea pallida* and *Echinacea angustifolia*. Overall, more than 20 RCTs have been conducted on the three species of echinacea, but more recent, higher-quality studies have shown very modest (such as decreasing cold symptom duration by one-half day over a week) to no benefit.^{31,32} Other botanicals are on the horizon with data suggesting benefit.

Andrographis paniculata is a plant from Asia that has traditional use in Ayurvedic medicine. Systematic reviews show that, collectively, *Andrographis* is superior to placebo in treating ARI symptoms,³³ and more recent trials have also shown benefit.³⁴ A typical dose is 300 mg (tablet or capsule, standardized to 4% andrographolide) four times a day during early ARI symptoms. This should then be stopped after ARI symptoms subside.

Elderberry (*Sambucus nigra*) is widespread in the Northern hemisphere, and the syrup extract of the berries may be helpful for ARIs and influenza-like illness. Only one RCT shows benefit in reduction of symptoms among 60 volunteers in a European trial.³⁵ A recent investigation found that elderberry was in fact active against influenza in an in vivo animal study.³⁶ The suggested dose for adults is 1 tablespoon of liquid extract 3-4 times a day.

Pelargonium sidoides (Umckaloabo) is a South African Geranium plant that has been used traditionally in that region for the treatment of ARIs among other things. Six RCTs show benefit, including a positive review in Cochrane Database.³⁷ One commercial product (Umcka) is listed as a 1X homeopathic preparation. Recommended dose is 1 mL 3-4 times a day for the duration of the cold. This particular brand was tested both in vivo and in vitro and found to have antiviral activity with improved outcomes among influenza infected mice.³⁸

Probiotics are an increasingly interesting area of research, particularly with *Clostridium difficile* gut infections and antibiotic-associated diarrhea. However, it was found incidentally to have some benefit with ARIs. A more recent RCT in 2011 found that taking *Lactobacillus plantarum* and *Lactobacillus paracasei* reduced days of ARI symptoms from 8.6 days in controls to 6.2 days in the treatment group. Furthermore, the incidence of ARIs was reduced from 67% in controls to 55% in the probiotic group.³⁹ Practically speaking, it is reasonable to recommend taking a probiotic capsule twice a day either at the onset of symptoms or ongoing for prevention.

Vitamin C and zinc are somewhat controversial and show mixed evidence for relief of ARIs, but they

appear to have some benefit. One RCT found that patients with the common cold who took 1000 mg of vitamin C and 10 mg of zinc had significantly reduced symptoms over 5 days of treatment. Vitamin C and zinc are very safe and well tolerated and are good options to recommend for most patients with ARIs.⁴⁰ However, caution should be used with Zicam, an herbal homeopathic combination over-the-counter nasal spray that can cause long-term olfactory dysfunction and loss of smell. One study found that Zicam was cytotoxic to sinus and olfactory nasal tissue.⁴¹

Oscillococcinum is a homeopathic medicine produced in and widely used in France and more than 50 countries for the treatment of influenza. It is an ultra-diluted, homeopathic-prepared remedy comprised of duck liver and heart to a ratio of 1:10400.⁴² A Cochrane Database review of six studies concluded that although considered very safe, there is insufficient good evidence to recommend Oscillococcinum for the treatment of ARIs. However, this review did not rule out the possibility that Oscillococcinum may be helpful clinically.⁴³ When presenting options to patients diagnosed with influenza and influenza-like illness, it is reasonable to support patients who elect to add Oscillococcinum as an adjunctive therapy.

SUMMARY

Although ARI is considered a nuisance illness, it is prevalent and widespread, with significant negative effects on quality of life. Treatment recommendations should focus on offering patients choices to create a meaningful health plan that addresses individual concerns using safe therapies. It is important to steer patients away from ineffective and potentially harmful therapies such as antibiotics. It is also important to offer empathy and partner with patients, which itself has a beneficial effect on symptom relief and quality of life. ■

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AGING

Exercise and Brain Health: Food for Thought?

By Nancy J. Selfridge, MD

Associate Professor, Integrated Medical Education, Ross University School of Medicine, Commonwealth of Dominica, West Indies

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The number of people in the United States age 65 and older has grown from 35 million in 2000 to 40 million in 2010, a 15% increase.

This number is expected to be about 55 million by 2020, a 36% increase for the coming decade.¹ Decline in cognitive health, just like many other

aspects of health, is associated with aging and exists on a continuum from normal functioning to mild measurable impairment to dementias such as Alzheimer's disease (AD). The health burden of mild cognitive impairment on individuals and society is hard to estimate, but AD currently afflicts one in eight people age 65 and older and has become the fifth leading cause of death in this age group. If present trends continue, it is estimated that as many as 16 million people will have AD by 2050 and health care costs related to this disease will increase from a current \$183 billion to more than \$1.1 trillion. The Centers for Disease Control and Prevention (CDC) reported in its most recent 2010 HealthStyles survey of 4183 U. S. adults that 70% of respondents expressed concern about memory loss and 20% feared becoming cognitively impaired.² Thus, identification of modifiable risk factors in the development of cognitive decline and dementia is important to stem the tide of this evolving problem.

BACKGROUND

Exercise and physical activity are known to positively affect many of the common consequences of aging, including loss of muscle mass and strength, diminished bone density, impaired balance, reduced cardiorespiratory endurance, and increased incidence of chronic debilitating illnesses such as cardiovascular disease and diabetes mellitus.³ A substantial body of both animal and human research suggests that exercise also appears to have a salutary effect on aspects of cognitive health, the components of which include: language, thought, memory, executive function, judgment, attention, perception, remembered skills, and the ability to live a purposeful life.^{2,5,6} However, variability in research design and rigor has prevented the CDC and other agencies from developing clinical guidelines or recommendations for preserving cognitive functioning with exercise.²

MECHANISM OF ACTION

Several mutually compatible hypotheses exist for the beneficial mechanisms of physical activity and exercise on cognitive function in health and in dementia. One of the hallmarks of AD is amyloid β plaque deposition in the brain. Laboratory studies have shown reduced amyloid β plaque formation in mice provided exercise interventions compared to sedentary mice. In humans, amyloid β brain load, plasma concentration, and serum levels have been shown to be lower in individuals with higher exercise and activity levels. These effects may be mediated by the ability of exercise to raise neurotransmitter levels (see below), increase testosterone levels, and increase growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1). Increase in cerebral blood flow associated with

Summary Points

- Exercise has several neurophysiological effects that may improve brain health, including increasing neurogenesis, angiogenesis, blood flow, and neurotransmitter levels.
- Epidemiological studies suggest that exercise has a protective effect against normal cognitive decline in aging and may prevent or postpone the onset of dementia.
- Interventional studies also suggest a role for exercise in preserving brain health in aging adults, but more rigorous evidence is needed before clinical guidelines can be made.

exercise also may play a role.⁴

Apart from an effect on amyloid β deposition, the increase in BDNF and IGF-1 may reduce brain atrophy (normal hippocampal volume loss is 1-2% per year in older adults) and may even increase brain mass and volume. BDNF is known to be associated with neurogenesis and increased survival of neurons, and IGF-1 mediates both exercise induced angiogenesis and neurogenesis. In fact, higher levels of fitness in older adults have been associated with increased mass in the frontal and hippocampal areas of the brain. Exercise causes significant increases in several neurotransmitters including serotonin, norepinephrine, acetylcholine, dopamine, and epinephrine, all of which are known to decline with aging.^{4,5}

Telomeres are nucleotide sequences on the ends of chromosomes that protect their integrity. Telomeres shorten with each successive cell division and eventually lose their protective effect. Thus, progressive telomere shortening leading to cell and tissue growth arrest, damage, and senescence is one of the main theoretical mechanisms of physical and mental decline due to aging.⁶ Telomerase is a ribonucleoprotein complex that preserves telomere length in proliferating cells. Telomerase activity appears to be upregulated in exercising mice and humans.⁷

Sex hormones may have a neuroprotective effect, and the increases in testosterone levels seen with exercise may play a role in preserving and improving cognitive function. Exercise may help reduce serum cortisol levels, one of the few hormones that increases with age and which may have a role in declining hypothalamic function with aging.⁷

Insulin resistance and type 2 diabetes have been implicated as having roles in AD because of the way

that they alter amyloid β processing. Exercise has a profound effect in improving insulin sensitivity and some of its beneficial effects on cognition may be mediated by this mechanism.⁴

The APOE $\epsilon 4$ allele has been associated with the strongest risk of late onset AD. Carriers of this allele are more susceptible to amyloid deposition if they are sedentary, but in exercising individuals the allele does not appear to increase brain amyloid load.⁴

CLINICAL RESEARCH

Summary of Epidemiological Studies. Several epidemiological studies have shown that exercise improves or helps maintain cognitive function. Most of these studies have assessed physical activity levels using self-reporting questionnaires but some have measured physical fitness or have made objective measures of physical activity with the use of an accelerometer device to measure body movement. Brown et al provide a systematic review of these.⁴ In one cross-sectional study of 1927 healthy adults ages 45-70 years who self-reported their physical activity, Angevaren et al found higher intensity physical activity was associated with better processing speed ($P < 0.01$), memory ($P < 0.05$), mental flexibility ($P < 0.05$), and overall cognitive functioning ($P < 0.01$). In another cross-sectional study, Barnes et al noted higher global cognitive function in 349 healthy subjects 55 years of age and older who had higher levels of measured cardiorespiratory fitness measured by peak oxygen consumption, exercise duration, and oxygen uptake efficiency using a standard treadmill exercise test. Six longitudinal studies in older adults ($n = 36,472$) reported a statistically significant positive impact on cognitive measures or a reduction in cognitive decline with higher levels of physical activity or an increased risk of cognitive decline in subjects with lower levels of physical activity. P values, when reported for these studies, ranged from 0.02 to 0.001. Two prospective cohort studies by Wilson et al reported no association between self-reported physical activity and incident AD, but there are possible explanations for these negative findings. Both of these studies used smaller sample sizes than other epidemiological studies demonstrating an effect, both had follow-up periods of < 5 years and one of the studies used subjects from a limited and non-representative demographic.⁴

Sofi et al conducted a meta-analysis of 15 prospective cohort studies that included 33,816 initially healthy older individuals of which 3210 developed cognitive decline. Exercise conferred a significant protective effect on cognitive function. Follow-up periods ranged from 1 to 12 years. The highest levels of exercise, measured in various ways in all of these studies (see conclusions, below)

provided the greatest protective effects (hazard ratio 0.62; 95% confidence interval [CI] 0.54-0.70; $P < 0.00001$); however, even low-to-moderate levels of exercise were beneficial compared to a sedentary lifestyle (hazard ratio 0.65; CI 0.57-0.75; $P < 0.00001$).⁸

Hamer et al reviewed data from 16 studies assessing the impact of physical activity on neurodegenerative disease risk ($n = 163,797$). In their analysis, the relative risk of dementia in the highest physical activity groups compared to the lowest activity or control groups was determined to be 0.72 (CI 0.60-0.86; $P < 0.001$) and the relative risk of AD was determined to be 0.55 (CI 0.36-0.84; $P = 0.006$). Again, exercise levels in these studies were measured and reported in highly variable ways.⁹

In a recent observational study of 104 early-stage AD patients, Winchester et al noted that sedentary patients experienced a significant decline in mini-mental status exam (MMSE) scores, while active patients had an attenuation in global cognitive decline. Those patients who walked for more than 2 hours per week demonstrated a significant improvement in MMSE scores over 1 year.¹⁰

In another observational study, Kattenstroth et al reported that subjects who maintained a regular schedule of dancing into old age had better cognitive, motor, and perceptual abilities compared to education-, gender-, and age-matched controls having no history of dancing or sports participation activities.¹¹

Summary of Intervention Studies. Brown et al summarized seven intervention trials assessing the impact of physical activity or exercise on cognitive function in healthy older adults. The interventions in these studies varied widely in type (strength, balance, stretching, aerobic, or combination), intensity, and duration of exercise. All provided supervised exercise, sometimes in group training and sometimes in a home-based program. All studies included men and women subjects; follow-up periods ranged from 6 months to 18 months, and several different measures of cognitive function were used as outcome measures. All but one of these studies demonstrated statistically significant or clinically significant improvement in cognitive performance in subjects after the exercise intervention.⁴

In a summary of eight studies of exercise intervention in subjects with cognitive decline, van Uffelen et al noted a statistically significant ($P < 0.05$) beneficial effect of exercise on cognitive decline in two-thirds of these studies. Again, the exercise interventions varied widely in type and volume as did the outcome

measures. Attendance/adherence and drop-out rates in intervention and control groups were not reported or not included in intention-to-treat analysis of data in a number of these studies.¹²

In results from the Austrian Stroke Prevention Study, Sen et al assessed MRIs in 725 elderly community-dwelling subjects for brain parenchymal fraction (a measure of brain atrophy) and volume of white matter lesions (a measure of ischemic cerebral damage), and compared these measures to individuals' fitness represented by VO_{2max} . VO_{2max} was inversely associated with white matter lesion volume in men ($P = 0.02$). There was no relationship between fitness level and brain parenchymal fraction in this study.¹³

In a randomized controlled trial assessing the impact of chronic endurance exercise training (supervised exercise, 3 hours per week for 23 months) in community-dwelling older adults ($n = 120$) in Italy, Muscari et al reported that MMSE scores decreased significantly in the non-exercising control group (mean difference -1.21 , CI -1.83 to -0.60 , $P = 0.0002$) though not significantly in the intervention group (-0.21 , CI -0.79 to 0.37 , $P = 0.47$). Odds ratio for the exercising adults to have stable cognitive status at the end of 1 year compared to the control group was 2.74 (CI 1.16 - 6.48) after adjustment for possible confounders.¹⁴

CONCLUSION

Though epidemiological evidence appears to support regular exercise and maintenance of physical fitness for reducing risk of cognitive decline due to aging, interventional studies are not yet numerous nor robust enough to support the development of clinical guidelines for exercise as a lifestyle strategy to preserve cognition by the CDC. Studies to date have had significant methodological flaws.

Most of the longitudinal or cross-sectional epidemiological studies have used self-report questionnaires to measure exercise and activity levels, a notoriously unreliable way to gauge physical activity or fitness levels. Further, the questionnaires have not employed consistent definitions of low, moderate, and high levels of physical activity and exercise. These two shortcomings create a significant problem when trying to determine what levels and types of exercise are most effective for preventing cognitive decline. Some of the studies have used an accelerometer device or measures of physical fitness that sidestep this dilemma to a degree. But even measures of physical fitness, such as the VO_{2max} or oxygen consumption, require maximal treadmill or cycle ergometer exercise tests wherein subjects are required to run or cycle until they reach

their maximal power; the test is terminated when the subject reports exhaustion or the supervising physician orders it for medical reasons. Thus, even these measures may be strongly influenced by subjective sensations and motivation. Many diverse tools have been used in these studies to measure cognitive functioning and different outcomes chosen, as well. Some have looked at level of cognitive function, some at cognitive decline, and others have used a diagnosis of AD as an outcome. The clinical significance of outcomes is important and needs to be considered and addressed in all studies, but often is not. An increase in a point or two on the MMSE score, for example, may take a person out of the range associated with early dementia (less than 21) or mild cognitive decline (21 to 24). Further, since not all cognitive decline results in functional impairment and not all cognitive decline in aging results in dementia, results and conclusions are difficult to compare and interpret clinically.

The interventional studies to date have looked at the effect of exercise both on healthy elderly and in persons already afflicted with dementia. These studies have employed very diverse exercise interventions ranging from "individualized programs," to purely aerobic programs in prescriptive weekly doses, to combinations of aerobic, strength, balance, and flexibility training. Volumes of exercise interventions have varied as have durations of the interventions. As previously mentioned, some of the interventional studies have failed to report adherence and dropout rates and some have failed to perform intention-to-treat analysis on data. In some instances, the control group was sedentary, and in others the control group also exercised or took part in some other non-exercise group activity, helping to control for group effect on outcomes. Again, cognitive function measures were very diverse and comparisons and clinically relevant conclusions are difficult to discern.

RECOMMENDATIONS

Exercise for middle aged and elderly people has proven benefit for prevention and attenuation of many chronic diseases strongly supported by research evidence. Larger and better designed interventional studies addressing the precise types and volumes of exercise needed to prevent cognitive decline or dementia are necessary before clinical guidelines can be made for exercise as a lifestyle intervention for these problems, though. Nonetheless, because of the low cost and low risk of increasing physical activity, physicians may counsel their aging patients that among other health benefits accumulating 150 minutes per week of moderate exercise according to present clinical guidelines may help promote brain health and prevent decline in

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cognitive function while we await the research supporting definitive guidelines for this specific benefit. ■

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CME QUESTIONS

1. Problematic traits of popular diets include:

- a. promises of losing specific amounts of weight in certain time periods.
- b. prioritizing one particular food or food group.
- c. providing a lot more testimonials than scientific evidence.
- d. All of the above

2. The recommended rate of weight loss in evidence-based guidelines is:

- a. 1-2% of body-weight per week.
- b. 1-2 pounds per week.
- c. 10-12 pounds per week.
- d. 10-12 percent of body-weight per month.

3. The current evidence regarding grapefruit suggests that:

- a. grapefruit should never be consumed by those taking statins.
- b. grapefruit consumed before meals dramatically increases weight loss.
- c. grapefruit is a nutritious and healthy food.
- d. grapefruit should be avoided by most people seeking to lose weight.

4. Which one of the following is *not* effective in managing ARI symptoms?

- a. Handwashing
- b. Zinc and vitamin C supplementation
- c. Supplementing with probiotics
- d. Long distance running

5. According to epidemiological studies, higher levels of physical activity in older adults may be related to cognitive function in which of the following ways?

- a. Reduced incidence of Alzheimer's disease
- b. Better scores on measures of cognitive function
- c. Improved cerebral blood flow
- d. All of the above

6. Which of the following is a proposed mechanism by which exercise may benefit cognitive function?

- a. Preservation of telomere length
- b. Increased neurogenesis
- c. Increased angiogenesis
- d. Increased neurotransmitter levels
- e. All of the above

[IN FUTURE ISSUES]

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