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Grapefruit Seed Extract as an Antimicrobial Agent

By **Dónal P. O'Mathúna, BS (Pharm), MA, PhD**

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RESISTANCE TO ANTIBIOTICS CONTINUES TO POSE A SERIOUS PROBLEM in treating infections. While new pharmaceutical agents are being developed, interest in alternative treatments is also growing. Grapefruit seed extract is one commercially available antimicrobial that has attracted considerable attention.¹ Manufacturers and other popular resources claim it is safe and effective for internal and external treatment of acne, allergies, athlete's foot, candida, the common cold, cold sores, various infections, sore throat, and thrush.² It is advertised in particular for women to treat yeast infections like vaginal candidiasis or thrush.

Grapefruit seed extract is sometimes abbreviated as GSE, but so is grape seed extract. The two supplements should be clearly distinguished from one another as their source and uses are completely different.

Background

Grapefruit seed extract is made from the seeds, pulp, and white membranes that remain after grapefruits are pressed to remove their juice. The leftover material was originally fed to cattle and pigs, and it was noticed that these animals seemed to get fewer infections. A number of methods have been used to extract the leftover plant material, but many of them are protected as proprietary information.³ These range from simply soaking the plant material in alcohol or another solvent, to complex processes that include high temperatures and the addition of ammonium chloride and acids.¹ The extract was initially used as an environmentally friendly antimicrobial spray for fruit and vegetables.⁴ However, controlled trials have found it to vary widely in its effectiveness when sprayed on foods.³ After being found to be safe, the extract was marketed as a dietary supplement with a reputation for treating bacterial, viral, and fungal infections in humans.

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Pharmacology

The extract is known to contain numerous polyphenolic compounds (such as hesperidin and resveratrol) and quaternary ammonium compounds.¹ An early study found that a commercial extract was active against 794 strains of bacteria and 93 strains of fungi.⁵ Another commercial extract was found to be active against 67 biotypes of gram-positive and gram-negative bacteria.¹ An alcoholic extract made by the researchers themselves was tested against 20 bacterial strains and 10 yeast strains.⁶ The extract was active against all microbes in the broth dilution test, but on agar plates the extract was not active against gram-negative bacteria, yet was active against gram-positive bacteria and yeast. A Norwegian commercial extract has more recently been shown to be active against the bacteria causing Lyme disease.⁷

Mechanism of Action

Electron microscopy of bacteria treated with grapefruit seed extract revealed disrupted bacterial membranes, which is believed to be the extract's mechanism of action.⁸ This is also the accepted bactericidal mechanism of action for quaternary ammonium salts.² Quaternary ammonium compounds are a class of compounds that include synthetic antimicrobials like benzethonium chloride and benzalkonium chloride. These are approved as disinfectants and antiseptics for use on hard surfaces and topically on humans.⁹ They are not approved as food additives in the United States or Europe, although they are in Japan.

Clinical Studies

The only clinical research readily located was published in 1990 and involved a commercial grapefruit seed extract.⁵ The publication reported two open-label trials involving patients with severe atopic eczema with accompanying gastrointestinal problems. Ten patients took 200 mL of a 0.5% solution twice daily for one month. The researchers reported that the patients had great difficulty taking the oral liquid because of its bitter taste. No significant changes occurred in fecal microflora testing with only two of 10 patients reporting intestinal improvements. The second trial gave 15 patients three 50 mg extract capsules three times daily for one month. The researchers reported significant antimicrobial activity against two pathogenic intestinal microorganisms, slight activity against three other microbes, and none against two others. No statistical analyses were reported. All 15 patients reported subjective improvements in their gastrointestinal symptoms, with no adverse effects.

Problematic Aspects

A serious problem with some commercial grapefruit seed extracts was revealed initially in 1999. Researchers at a German Institute of Pharmacy tested six commercially available grapefruit seed extracts.¹⁰ Five of the six products showed strong antimicrobial activity against a range of bacteria, yeast, and other microbes. However, further analysis of these five active samples found they contained between 1.25% and 10% benzethonium chloride. Three of the samples contained 0.012-0.025% triclosan and three contained methyl paraben (both are synthetic antimicrobials). The one sample which contained no benzethonium chloride also showed no antimicrobial activity. The researchers made their own grapefruit seed extract and it had no antimicrobial activity. A subsequent study was conducted to develop methods of easily separating the three synthetic compounds identified above. Of nine commercial grapefruit seed extract products purchased in the United States, seven contained benzethonium chloride (0.3-22%), three contained triclosan (0.01-1.13%), and none contained methyl paraben.¹¹

One manufacturer claimed that what was identified as benzethonium chloride was a different quaternary ammonium compound formed during their extraction process.³ A subsequent analysis by a research laboratory in the U.S. Department of Agriculture found 8% benzethonium chloride in a commercial liquid grapefruit seed extract.³ The compound's identity was confirmed by several independent tests. Even higher concentrations of benzethonium chloride were found in powdered sam-

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ples, leading the researchers to conclude that the chemical was unlikely to have been formed in such concentrations during extraction or processing of the grapefruit.

The same Department of Agriculture laboratory tested another commercial grapefruit seed extract and found it contained 22% benzalkonium chloride (BAC).² BAC is a mixture of three closely related synthetic compounds widely used as a disinfectant and sanitizer, but not recommended for internal use. Poisonings have occurred when people have ingested products containing more than 10% BAC, and allergic reactions occur, especially in asthmatic patients.² The researchers concluded that it was “unlikely” that 22% BAC could have formed during the processing of grapefruit seeds.

Another investigation was conducted into grapefruit seed extracts used in farming as organic antimicrobial sprays.⁴ Nine products were tested, of which seven contained various synthetic chemicals, most commonly benzethonium chloride. One of the “grapefruit seed extracts” that contained no synthetic antimicrobials also contained no grapefruit extract but was made from three other herbs.

In the most recent analysis published, 41 various products were purchased in Japan.¹² These included food additives, cosmetics, dietary supplements, and disinfectant sprays. All but three contained one or more synthetic antimicrobials. One food additive contained 39% benzethonium chloride.

The effects of consuming grapefruit seed extract containing these preservatives are unknown. An investigation was triggered in Sweden when two patients, a married couple, had complications related to warfarin.¹³ Both patients had been stabilized on warfarin for years without problems. Three days after taking grapefruit seed extract, one patient developed a minor subcutaneous hematoma. Bleeding times were elevated in both patients and returned to normal when the grapefruit seed extract was stopped. The medical team had the grapefruit seed extract analyzed along with two other commercial products. The three samples contained no trace of grapefruit, but consisted of glycerin, water, and benzethonium chloride. An extract prepared from grapefruit seeds by the analytical laboratory contained no benzethonium chloride. Further testing revealed that benzethonium chloride and the commercial extracts were strong inhibitors of the cytochrome P450 enzyme that metabolizes warfarin, as well as many other drugs.

Conclusion

Grapefruit seed extracts have been found to be broad-spectrum antimicrobial agents. However, considerable questions have been raised by independent analyses as

to whether this activity is natural or due to adulteration. A number of different synthetic antimicrobial agents have been found in commercial products, sometimes in very large concentrations. Inconsistent findings have also been reported where freshly prepared extracts have sometimes had antimicrobial activity but sometimes have not. Manufacturers consistently deny that their products are deliberately adulterated. However, even if the quaternary ammonium compounds are produced during processing, almost no clinical research has been conducted on these products for human use. The small number of studies using the extract as an agricultural antimicrobial spray have not produced consistent results.

Recommendation

Given the numerous findings of synthetic antimicrobials in grapefruit seed extracts, people should avoid consumption of these products. One of the remarkable features of this saga is that problems like those in Sweden have not been reported more often. This may be because grapefruit seed extract is usually taken after being diluted significantly because of its extremely bitter taste. It may also be possible that people do not suspect that complications with pharmaceuticals could be related to supplements they are taking. Given that some of these synthetic antimicrobials are approved for use in no-rinse hand washes, topical use of grapefruit seed extract on unbroken skin may not be problematic. Whether it prevents transmission of infections remains uncertain. ❖

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Does Lowering Gamma-tocopherol Explain the Failure of Vitamin E Supplementation Trials?

ABSTRACT & COMMENTARY

By **Diane L. McKay, PhD, FACN**

Dr. McKay is an Assistant Professor at the Friedman School of Nutrition Science and Policy, and conducts research at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University; she reports no financial relationship to this field of study.

Synopsis: *Several large observational studies have suggested that vitamin E supplementation lowers the risk of coronary heart disease. However, the results of large randomized controlled trials failed to show a clear benefit of α -tocopherol supplementation on cardiovascular outcomes. In this study, supplementation with high-, medium-, and low-doses of α -tocopherol, plus vitamin*

C, decreased plasma γ -tocopherol in type 2 diabetics, but did not affect markers of oxidative stress, inflammation, or hypercoagulation following an atherogenic test meal. The findings suggest that α -tocopherol supplementation suppresses the beneficial effects of the γ -tocopherol isomer. Although the health impact of lowering plasma γ -tocopherol is an issue that requires further investigation, the authors' overall conclusions are unwarranted due to the marked limitations of their study.

Source: Gutierrez AD, et al. The response of gamma vitamin E to varying doses of alpha vitamin E plus vitamin C. *Metabolism* 2009;58:469-478.

A RANDOMIZED, CROSSOVER STUDY WAS CONDUCTED TO determine if supplementation with α -tocopherol and vitamin C lowered plasma levels of γ -tocopherol in a dose-dependent manner, and whether these changes affected surrogate markers of atherosclerotic risk following a high-fat meal. Subjects, including six men and six women (mean age, 53 years; BMI, 29 kg/m²) with well-controlled type 2 diabetes (mean duration, 9 years), were randomized to receive either no vitamins, low- (200 IU α -tocopherol + 250 mg vitamin C), medium- (400 IU α -tocopherol + 500 mg vitamin C), or high-dose vitamins (800 IU α -tocopherol + 1 g vitamin C) for a period of two weeks each. At the end of each treatment period, subjects were given an atherogenic high-fat test lunch, equivalent to a McDonald's Big Mac meal. Plasma levels of α - and γ -tocopherols (lipid-adjusted), as well as markers of oxidative stress (oxidized LDL, malondialdehyde, erythrocyte glutathione peroxidase), atherosclerotic risk (non-esterified fatty acids), inflammation (C-reactive protein, adiponectin, interleukin-6), and hypercoagulation (plasminogen activator inhibitor-1, fibrinogen) were assessed just prior to the meal and for five hours during the postprandial period.

After two weeks, a dose-dependent elevation in lipid-adjusted α -tocopherol levels was observed with the high-, medium-, and low-dose vitamins compared with the no-vitamin control. However, a 50% reduction in lipid-adjusted plasma γ -tocopherol was observed at all three doses of α -tocopherol, indicating a threshold effect at or below the 200 IU dose. No significant between-group differences were observed for any surrogate markers, measured at the end of the two-week treatment period and again postprandially, when compared with the no-vitamin control. The authors conclude that the reason α -tocopherol supplementation had no effect on markers of atherosclerotic risk can be explained by the suppressed levels of circulating γ -tocopherol.

■ COMMENTARY

Vitamin E is not a single molecule, but rather a group of eight isomers, including four tocopherols (α -, β -, γ -, δ -tocopherol) and four tocotrienols (α -, β -, γ -, δ -tocotrienol). Most vitamin E dietary supplements contain only α -tocopherol, while approximately 70% of the vitamin E from food sources in the United States is in the γ -tocopherol form, largely due to the high intake of soybean and other vegetable oils, including canola oil, in the American diet.¹ Although the ratio of γ - to α -tocopherol is relatively high in the diet, it is essentially reversed in plasma. This is attributable to the preferential uptake of α -tocopherol by the hepatic α -tocopherol transfer protein. Because α -tocopherol is the predominant form of vitamin E found in plasma and tissue, it has been studied more extensively, both in vitro and in vivo, and serves as the “reference” form for achieving vitamin E requirements in humans.

All forms of vitamin E have some antioxidant activity. Recent data indicate that the different vitamin E forms also have other bioactivities unrelated to their antioxidant activity, including anti-inflammatory and immunostimulatory properties, which may also be important for maintaining and improving human health.² In fact, several distinct molecular targets are thought to be involved in the anti-inflammatory effects mediated by α - and γ -tocopherol. For example, γ -tocopherol is a stronger inhibitor of cyclooxygenase in vitro, and possibly lipoxygenase, than α -tocopherol. Furthermore, γ -tocopherol traps reactive nitrogen species in vitro more efficiently than α -tocopherol. While both tocopherols exhibit anti-inflammatory activity in vitro and in vivo, supplementation with mixed tocopherols seems to be more potent than supplementation with α -tocopherol alone.²

It is well known that supplementation with α -tocopherol alone lowers plasma levels of γ -tocopherol, and studies exploring the potential consequences of this relationship are warranted. In this study by Gutierrez et al, type 2 diabetics, with presumably elevated oxidative stress levels, were supplemented with RRR- α -tocopherol at levels eight- to 36-fold higher than the RDA for two weeks to determine whether there is a dose-response relationship with plasma γ -tocopherol levels. The fact that all doses used in this study lowered plasma γ -tocopherol equally suggests a threshold effect and that the range of doses was insufficient to draw any meaningful conclusions regarding whether a true dose-response effect exists. Moreover, the authors report only post-supplementation levels relative to the no-vitamin control group, a critical flaw, and did not report whether there were any changes in plasma vitamin E levels between

the pre- and post-supplementation period. Nor did they include any washout period between each arm of this crossover study. This, too, is a serious flaw as steady-state vitamin E status in tissues typically takes at least four weeks to achieve. Furthermore, no information on the vitamin E content of subjects' background diets prior to supplementation, or changes during the supplementation period, is provided. Previous studies have shown that subjects' response to vitamin E supplementation depends on their initial status, as well as their dietary intake, neither of which was considered in this study design.

A second objective of the Gutierrez et al study was to determine whether several biomarkers of atherogenic risk were affected after challenging supplemented subjects with a high atherogenic meal to further elevate their oxidative stress. An earlier study demonstrated that a single high-fat meal significantly reduced flow-mediated dilation (FMD), a measure of endothelial function, for up to four hours in healthy subjects, and no reduction was observed when vitamins C (1 g) and E (800 IU) were administered with the same meal, suggesting a potential oxidative mechanism.³ Gutierrez et al correctly note that type 2 diabetic patients show greater oxidative stress in response to a standardized meal when compared with healthy subjects. However, they fail to consider that these patients may also require a higher dose of antioxidant supplements, or a longer duration of treatment, to counteract the elevated stress. Interestingly, it was recently determined that vitamin E in doses of at least 1,600 IU/d for 16 weeks were necessary to suppress F2-isoprostane levels, a validated measure of oxidative stress, in individuals at risk for cardiovascular disease.⁴

Gutierrez et al conclude that the absence of an effect on all biomarkers with every level of α -tocopherol supplementation used in their study was due to the lowering of plasma γ -tocopherol levels. Within the context of their study this conclusion is inappropriate as it could not be drawn from the experimental design, e.g., it is just as likely that their findings were due to the increase in plasma or tissue α -tocopherol or vitamin C. However, it is more likely that their subjects were well-nourished, and that the magnitude of change in their vitamin E status after two weeks of supplementation was minimal and had little influence on these biomarkers in the short duration of this intervention. This is supported by the fact that there were no significant differences between groups, including the no-vitamin control group, with regard to any of the oxidative stress biomarkers prior to administering the high-fat meal.

In a pooled analysis of several cohort studies, the

increased consumption of total vitamin E and dietary vitamin E were each associated with a significantly lower risk of CHD, while vitamin E supplementation was not.⁵ Likewise, the results of large randomized controlled trials failed to show a clear benefit of α -tocopherol supplementation on cardiovascular outcomes.⁶ There are several plausible explanations for these discrepant findings, and the role of plasma γ -tocopherol should certainly be considered. However, based on the findings of Gutierrez et al, it cannot be concluded that the failure of the large trials was due to a reduction in γ -tocopherol. The authors appropriately point out that the lack of well-standardized γ -tocopherol supplements, absent the α -isomer, limits research into this relationship, and that further studies are warranted. ♦

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Tea Time Down Under: HIV

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *In-depth laboratory analysis suggests that human semen (SE) contains a peptide that enhances HIV infectivity, but the green tea polyphenol epigallocatechin-3-gallate (EGCG) inhibits the increased infectivity associated with the peptide. This raises the possi-*

bility that topical intravaginal EGCG could be a useful adjunct in controlling the spread of HIV infection.

Source: Hauber I, et al. The main green tea polyphenol epigallocatechin-3-gallate counteracts semen-mediated enhancement of HIV infection. *PNAS* 2009;106:9033-9038.

THE AUTHORS OF THIS LABORATORY STUDY FOCUSED ON the possibility that green tea may contain constituents that reduce infectivity of the HIV virus. Prior study had shown that a peptide derived from prostatic acid phosphatase and present in high concentrations within SE enhanced HIV infectivity, apparently by creating amyloid fibrils (called semen-derived enhancer of virus infection, or SEVI). In a dose-dependent fashion, EGCG was first shown to interfere with amyloid fibrillogenesis, and a subsequent lab study showed that EGCG helped to trigger the degradation of pre-formed amyloid fibrils. In another test, the researchers employed ultrathin sectioning together with electron microscopy and found that incubation of SEVI fibrils with EGCG resulted in no damage to the fibrils after 12 hours, but extensive fibrillar degradation at 60 hours. Interestingly, EGCG exhibited little in the way of antiviral activity in the absence of SEVI. EGCG showed no untoward effects on uninfected cells. The authors conclude that EGCG targets and degrades the SEVI amyloid fibrils, thus interfering with otherwise enhanced HIV infectivity, and without toxic effects on healthy, non-infected cells.

■ COMMENTARY

The authors draw on prior data to show that SEVI may be an important HIV infectivity factor during sexual transmission, share new data suggesting a role for EGCG in counteracting the enhanced infectivity induced by SEVI fibrils, and suggest that the polyphenol may be an effective and inexpensive intravaginal adjunct to more standard microbicidal therapy. Previous studies have suggested a possible role for ingested green tea to help control the spread of HIV infection, but this is perhaps the first study to explore such a role for a topical green tea EGCG extract. The researchers point out that EGCG is acid-stable, and thus should be stable in the intravaginal environment.

Around the world, infection with HIV most commonly occurs through sexual transmission. Current estimates are that 33 million people are infected with HIV, many of them poor. Imagine—a relatively benign and cheap intervention, developed from a readily available source (green tea), helping to lessen the infectivity of the HIV virus. Is more study needed? Yes, as the series of tests

reported here were all bench research, the results compel scientists to look at EGCG's potential effects in humans in an ethically sound manner. Though the mechanism by which EGCG interferes with SEVI fibrils is yet unknown, the results of this study are exciting since, as with most illness, any advance in primary prevention trumps advances in treatment of established disease. ❖

Ethnic, Racial, and Educational Differences in CVD and Diabetes Control — Can Insurance Coverage Mitigate Disparities?

ABSTRACT & COMMENTARY

By Susan T. Marcolina, MD, FACP

Dr. Marcolina is a board-certified internist and geriatrician in Issaquah, WA; she reports no financial relationship to this field of study.

Synopsis: Subgroups of U.S. adults who are minorities, poor, or undereducated with chronic cardiovascular risk factors such as hypertension, diabetes, and hypercholesterolemia have large disparities in treatment for these conditions compared with white, high school-educated adults when they are uninsured or underinsured. Such disparities adversely impact risk of significant morbidity and mortality from cardiovascular disease (CVD). Insurance coverage with Medicare after age 65, however, mitigates many disparities by virtue of expansion of access to medical and laboratory evaluation and therefore to subsequent dietary, pharmacologic, and diagnostic management strategies that optimize control of blood pressure as well as serum levels of glucose and cholesterol.

Source: McWilliams JM, et al. Differences in control of cardiovascular disease and diabetes by race, ethnicity, and education: U.S. trends from 1999 to 2006 and effects of Medicare coverage. *Ann Intern Med* 2009;150:505-515.

MCWILLIAMS ET AL EXAMINED DATA FROM THE National Health and Nutrition Examination Survey (NHANES) from 1999 to 2006 on a cross-section of more than 12,000 U.S. adults ages 40-85 years who either had diabetes, hypertension, coronary heart disease (CHD), or stroke, or had physical exam findings or labo-

ratory results that indicated the presence of these conditions. Disease control for each of these conditions was defined, according to standard recommendations, as hemoglobin A1C levels less than 7% among participants with diabetes,¹ average blood pressure less than 140/90 mmHg for those with hypertension, (though the Seventh Joint National Committee [JNC 7] on Prevention, Detection, Evaluation and Therapy of High Blood Pressure would consider individuals with systolic blood pressures of 120-139 mmHg or diastolic blood pressures of 80-89 mmHg as prehypertensive and in need of lifestyle modifications of sodium restriction, weight loss, and exercise to prevent CVD),² and total cholesterol levels less than 200 mg/dL for patients with diabetes, heart disease, or stroke.³ Over the eight years of this study, these authors showed that despite age- and sex-adjusted improvement in the control of blood pressure, hemoglobin A1C, and cholesterol levels, significant disparities existed for certain patient subgroups.

Black and Hispanic adults had significantly lower rates of blood pressure control (only 44% achieving BP goal, $P < 0.001$; and 42.5% achieving BP goal, $P < 0.001$, respectively), compared to white adults (52.8% at BP goal) with hypertension. Similarly, for adults with diabetes, levels of hemoglobin A1C were significantly higher with lower rates of glycemic control in black (only 41.6% reaching goal A1C level, $P < 0.001$) and Hispanic (only 37.8% reaching goal hemoglobin A1C level, $P < 0.001$) adults compared to white adults (58.1% achieving hemoglobin A1C goal). Mean systolic blood pressure and hemoglobin A1C levels were also significantly higher for less educated adults compared to more educated adults (140.8 vs. 138.4 mmHg, $P = 0.034$; and 7.6 % vs. 7.1%, respectively, $P < 0.001$). Thus, improved health care quality did not penetrate equally to different segments of the society.

Interestingly, however, McWilliams et al found that many health care disparities diminished significantly, though not completely, among participants 65 years of age or older, with Medicare insurance coverage. Whereas mean differences in systolic blood pressure between black and white study participants before age 65 was 7.0 mmHg, after age 65 and the access to care which Medicare brings to the minority, poor, and undereducated populace, this difference decreased to 2.8 mmHg. Control of diabetes was affected in the same way. Prior to age 65, the difference in mean hemoglobin A1C levels between whites and non-whites (black and Hispanic participants) was 0.9, whereas after age 65, this decreased to 0.2 ($P < 0.001$). The difference in mean hemoglobin A1C levels between non-high school graduates and graduates was 0.6% before age 65 and decreased to

0.1% after age 65 ($P = 0.033$). Furthermore, the group differences were greatest when comparisons of disease control measures were made before and after ages 65, 66, and 67, which strongly suggests the importance of Medicare acquisition to improved chronic cardiovascular disease control.

■ COMMENTARY

Given that coronary heart disease is the leading cause of death for both men and women in the United States⁴ and that several risk factors including hypertension, diabetes, and elevated serum cholesterol levels can be modified through diagnostic evaluation and dietary, lifestyle, and pharmacologic interventions to reduce mortality, morbidity, and, ultimately, cost of care, it is important to disseminate these disease-modifying interventions to all affected patients. It has been clear, however, that not all patients affected by chronic diseases have access to these same interventions that could improve their overall health, particularly when they lack insurance coverage.⁵ Since black, Hispanic, and less educated adults are generally more likely to be underinsured or uninsured, expansion of insurance coverage for these subgroups of patients may be of great benefit since it is known that patients without insurance delay seeking care due to concerns regarding expense, have more difficulty obtaining prescription medications, and receive less outpatient care and diagnostic testing.^{6,7} Certainly, Medicare acquisition after age 65 has been associated with decreased racial and socioeconomic differences in ability to obtain mammography and self-reported overall general health.^{8,9}

When Taiwan implemented a universal national health insurance in 1995, life expectancy improved in the lower-ranked health class groups that had higher mortality rates before introduction of national health insurance, particularly with regard to cardiovascular diseases. Prior to institution of national health insurance, CVD mortality caused the greatest disparity between the health class groupings. According to Wen et al, utilization of medical services by the lower-ranked health classes increased and disparity narrowed compared to the highest-ranked health group; however, cost remained at approximately 5-6% of the gross domestic product.¹⁰ This is in contrast to the situation in the United States wherein health care expenditures account for 16% of GDP despite the fact that 50 million U.S. residents are uninsured and health care disparities are prevalent, particularly among the poor, minorities, and undereducated citizenry.¹¹

McWilliams et al have provided data from a representative American population, which demonstrate that

access to Medicare, the universal public insurance for U.S adults older than age 65, improves control of blood pressure, glucose, and cholesterol levels, important modifiable risk factors for cardiovascular disease, the leading cause of death in the United States. In this reviewer's opinion, and as supported by data like those presented here, it is time to improve quality of care and lessen health care expenditures by expanding access to include all U.S. residents. The provision of a national health insurance plan to United States residents would be a cost-effective, long-term investment strategy since persons with diabetes, hypertension, and heart disease and those with risk factors for these chronic diseases experience the majority of the preventable morbidity and mortality among uninsured older adults.¹² ❖

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Omega-3 Fatty Acid Adds Little Benefit to Resistance Training for Older Adults

ABSTRACT & COMMENTARY

By **Dónal P. O'Mathúna, BS (Pharm), MA, PhD**

Synopsis: A randomized, double-blind study found that alpha-linolenic acid (an omega-3 fatty acid) supplementation provided few additional benefits for older adults participating in a 12-week resistance-training program.

Source: Cornish SM, Chilibeck PD. Alpha-linolenic acid supplementation and resistance training in older adults. *Appl Physiol Nutr Metab* 2009;34:49-59.

THE PURPOSE OF THIS RANDOMIZED, DOUBLE-BLIND, controlled trial was to evaluate whether alpha-linolenic acid (ALA) supplementation provides additional benefits during 12 weeks of resistance training in older adults. The hypothesis was that ALA might counteract the chronic low-grade inflammation that can contribute to decreased muscle mass and strength in older people.

The participants were 60 healthy, untrained adults older than 60 years of age (mean, 65.4 ± 0.8 years). They were randomly assigned to supplement their diet with either 30 mL flaxseed oil (containing about 14 g/day ALA) or 30 mL placebo (corn oil) for 12 weeks.

The oil was to be added to other foods. Fifty-one people completed the study, 28 men and 23 women. The resistance-training program involved 13 activities, which exercised all major muscle groups. Participants exercised three days a week and were monitored and supervised. The load in each exercise was increased as participants were able to complete all prescribed exercises.

Outcomes were measured at baseline and after 12 weeks. Blood samples were taken to measure cytokine levels, muscle strength was evaluated using maximum chest press and leg press, muscle thickness was measured by ultrasound of the knee and elbow flexors and extensors, and body composition was measured using dual energy X-ray absorptiometry.

ALA supplementation led to reductions in the concentrations of only one inflammatory cytokine, interleukin-6 (IL-6) and only among men, not women ($P = 0.003$). The supplements had minimal effect on muscle mass and strength during resistance training. While chest and leg press strength, lean tissue mass, muscle thickness, hip bone mineral content and density, and total bone mineral content significantly increased, and percent fat and total body mass decreased with the resistance training program ($P < 0.05$), the two groups differed from one another in only one outcome: The males in the ALA group had a significantly greater increase in knee flexor muscle thickness ($P < 0.05$). Total-body bone mineral density improved in the placebo group, with no change in the ALA group ($P = 0.05$).

■ COMMENTARY

Loss of muscle mass and strength is a significant problem for older men and women. Such loss has been linked with chronic low-grade inflammation. Increased concentrations of the inflammatory cytokines, tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), are associated with reduced muscle mass, strength, and fiber number in older adults. Strength training can improve muscle mass and strength, and preserve bone mass. Some, but not all, studies have found that resistance training in older adults also can increase the levels of anti-inflammatory cytokines.

ALA is an essential omega-3 polyunsaturated fatty acid, which acts as a precursor to other, longer-chain omega-3 fatty acids. However, the conversion from ALA to the other omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is quite inefficient. The relatively high ratio of omega-6 to omega-3 fatty acids in the Western diet is associated with an increased risk of chronic diseases, including inflammatory diseases.¹ Therefore, ALA supplementation has

been proposed as a method of reducing the risk of chronic inflammatory diseases. The hypothesis for this study was that ALA might have an additive effect on the benefits of resistance training. This would lead to both a reduction in the low-grade inflammation associated with aging and an increase in muscle mass and strength.

The study was well-designed and clearly reported, although with some limitations. The method of randomization was not reported, and intention-to-treat analysis was not used. Of the 60 participants who started, nine were lost to follow-up. Reasons for not completing the study were obtained. Only one person stopped for reasons to do with the study — an inability to tolerate the supplement. The study measured several outcomes, which could be problematic as multiple hypothesis testing can lead to positive findings due to chance alone. This was not a problem here as few measurements showed significant differences between the two groups.

The study found that older men, but not older women, had reduced levels of IL-6 after ALA supplementation with 12 weeks of resistance training. The TNF- α levels were reduced, but not to a statistically significant degree. A post-hoc power analysis showed that a much larger number of subjects would have been needed to show significant changes. The reason for the gender differ-

ences was not known.

The results of the study provided further data to demonstrate the value of resistance training for older adults. However, ALA supplementation did not add any further benefit. Even though supplementation reduced IL-6 levels in older men, only knee flexor muscle thickness showed additional benefits. However, it is possible that 12 weeks of supplementation is not long enough to show beneficial effects. Other omega-3 fatty acids such as EPA and DHA are more prevalent in fish oils and may have a greater anti-inflammatory effect compared to the flaxseed oil tested in this study. Such hypotheses would need to be tested in future studies.

The bottom line from this study is that patients can be encouraged to undertake at least three days of resistance training per week to help off-set loss of muscle mass and strength. This study provides little evidence that supplementation with ALA will provide additional benefits for musculature. While there is some evidence of an anti-inflammatory benefit for older men who take ALA and engage in strength training, further research is needed to confirm these findings. ❖

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CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

- After completing the program, physicians will be able to:
- a. present evidence-based clinical analyses of commonly used alternative therapies;
 - b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
 - c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

24. The most commonly found antimicrobial in grapefruit seed extracts is:
 - a. benadryl.
 - b. methyl paraben.
 - c. benzethonium chloride.
 - d. grapefruit juice.
25. Patients should be alerted to the possible contamination of grapefruit seed extracts based on:
 - a. one analytical study.
 - b. several analytical studies from around the world.
 - c. a number of randomized controlled trials.
 - d. anecdotal reports of patients' concerns.
26. Evidence of the effectiveness of grapefruit seed extracts as antimicrobials is based on:
 - a. in vitro studies on microbial agents.
 - b. anecdotal reports.
 - c. two open-label small trails.
 - d. All of the above

Answers: 24. c, 25. b, 26. d.

Itchy and Scratchy: Wool and Fibromyalgia

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *This brief pilot intervention trial grew out of data suggesting that symptoms of fibromyalgia are often worse during cold weather, and that the skin temperature associated directly with specific trigger points may be lower than in healthy subjects. Focusing specifically on the use of woolen undergarments and bedding, the results suggest that keeping warm during winter months may help ameliorate pain and enhance functionality in people with fibromyalgia.*

Source: Kiyak EK. A new nonpharmacological method in fibromyalgia: The use of wool. *J Altern Complement Med* 2009;15:399-405.

IN AN EXTRAORDINARY DISPLAY OF RESEARCH TENACITY, the author of this clinical intervention trial sought to determine whether the use of woolen undergarments and bedding during the winter months would have health implications for people in Turkey with fibromyalgia (FMS). A total of 50 adult female volunteer subjects who met the American College of Rheumatology's criteria for FMS were selected for the study, and were equally divided between the treatment and the control group, the groups being statistically similar to one another. Members of the treatment group were to wear woolen underwear that covered the body from the shoulders to the thighs, thus covering most trigger points, and to use a woolen bed liner, woolen quilt, and woolen pillow during the six-week trial that occurred between January and March. The control group subjects received cotton undergarments and bedding made of synthetic material.

Participants underwent pre- and post-intervention assessments that included a measure of pain using a visual analog scale (VAS), tender points count as determined by a specialist blind to treatment, and results of the Fibromyalgia Impact Questionnaire (FIQ, used to assess daily activity and FMS symptoms). The day following a subject's initial evaluation, the author personally visited the person's home and provided the treatment materials. She also made the subject's bed. The author subsequently visited each subject on a weekly basis for six weeks to ensure adherence to study protocol. Subjects were instructed to wear their garments constantly

and not to remove the specified bed linens. Study participants were also instructed to maintain a daily diary of treatment material use as well as medication use (analgesics and/or NSAIDs).

The mean duration of FMS was more than five years in this study population, the majority of whom were married, poorly educated, and unemployed. At the end of the trial, significant improvement was seen in members of the treatment group compared with the control group for degree of pain, tender point counts, and scores on the FIQ. Subjects in the treatment group also used less medication than those in the control group, and experienced more restorative sleep. The author concludes that the use of woolen clothing and bedding during cold weather reduces the symptoms of FMS.

■ COMMENTARY

Give this author a prize of some sort. I know plenty of people not enrolled in research trials who would be pleased to have someone come by their home to make their beds, even once!

Getting serious, theories abound but there is no universally accepted theory regarding the cause of fibromyalgia, nor its treatment. Many have noted that patients' symptoms of FMS seem to be worse during cold weather and better with higher ambient temperatures. In fact, the authors refer to data suggesting people with FMS have lower skin temperature at the site of tender points than healthy people, perhaps indicating decreased blood flow. Perhaps a practitioner's gentle admonition to "stay warm" might go a long way toward ameliorating some symptoms of FMS.

The author notes that animal wool has a higher capacity for retaining heat than plant or synthetic fibers, forms isolated air pockets, and is highly absorbent, capable of absorbing 30-50% of its weight in dampness, thus pulling sweat away from the body. The study emphasizes the use of woolen products, but it seems likely that seasonally appropriate garb and bedding could offer similar therapeutic benefit.

Leaving aside the memorable dedication of the author, there are some shortcomings of this pilot study. How the subjects were chosen is not clearly described, but the process does not appear to have been random, and the unique study population could impact generalizability, though this hardly seems a significant point.

Greater attention to details of lifestyle habits and dietary factors is finally becoming the norm in health care. For the setting of FMS, this study highlights a simple yet apparently effective lifestyle intervention requiring no prescription pad and minimal medical jargon. Simply say, "Stay warm." ❖

Survey released at ACOG meeting reports delay in pregnancy and annual check-ups

ACCORDING TO RESULTS OF A GALLUP ORGANIZATION survey released during the American College of Obstetricians and Gynecologists (ACOG) 57th Annual Clinical meeting in Chicago, women are delaying important preventive care—in the form of pregnancy and annual check-ups—as a result of the economy.

The survey was conducted on behalf of ACOG and its findings are similar to other recent reports on the economy's effect upon health care utilization, including a Kaiser Family Foundation survey that reported 15% of Americans have cut pills in half or skipped doses to put off refilling a prescription and 19% have delayed getting preventive care.

Gallup's on-line survey reached more than 1000 women ages 18-44, and found that the economy's effect on women has reached very personal and intimate areas of their lives, namely decisions about sex and family planning. Here are some of the survey results:

- Two-thirds of women (66%) ages 18-44 report that they have been affected, at least to some extent, by the country's economy, including 18% who say the nation's economy has affected them a great deal and 48% who say they have been personally affected to some extent. More specifically,
 - One in eight women (12%) says they have experienced a job loss as a result of the economy.
 - Six percent of women report having lost their health insurance.
 - Nine percent of women report they have taken on an extra job.
 - One in seven (14%) says they have postponed an annual ob-gyn check-up.
 - Fifteen percent report having cut back or stopped taking some medications because of the cost.
- The vast majority of women (88%) report that they have health care coverage.
- Compared to 12 months ago, roughly 10% of women currently using some form of birth control say they are worried they may not be able to afford it. Among women using a hormonal method of contraception, 13% report that they are worried that they may not be

able to pay for it.

- Among women currently using birth control, 12% report that they have switched or changed birth control methods in the past year. Of these women, 14% switched because of the cost, 18% changed because of a doctor's recommendation, and 38% switched due to health reasons.
- Only 3% of women report having stopped using a birth control method in the past year because they couldn't afford it. Among women currently using a hormonal method, this doubles to 6%.
- Women reported that, on average, having a reliable method of contraception is extremely important to them (a 9 on a 10-point scale).
- Compared to women who say that they have been affected at least to some extent by the country's economy, those women who say that they have been affected a great deal are more than twice as likely to report that they have decided to limit the size of their family (29% vs. 13%); are more than twice as likely to talk to their partner about having an unintended pregnancy (26% vs. 12%); and are more than three times as likely to postpone a planned pregnancy (15% vs. 5%).

For more details about this survey, please visit: www.acog.org. ❖

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