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CARDIOVASCULAR DISEASE

Is a Grapefruit a Day Good or Bad for the Heart?

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Dr. O'Mathúna reports no financial relationships relevant to this field of study.

Grapefruit is a popular fruit worldwide because it is tasty, nutritious, and increasingly viewed as healthy. The original grapefruit was "white" and very seedy, but varieties have been selected to give seedless and more red cultivars.[1] Health claims to date have focused on grapefruit's alleged ability to promote weight loss. The Hollywood diet was the first of these in the 1930s, and various formulations have followed. Recent studies into the effectiveness of these have found little support for the claims made.[2] Other basic and clinical research into grapefruit have focused on claims that grapefruit may protect against the risk of heart disease either due to the presence of antioxidants (especially vitamin C) or effects on blood lipids.[1] At the same time, concerns have been raised about detrimental interactions between grapefruit juice and drugs, especially statins. Most of the research in this area has been conducted on grapefruit juice, and whether the fresh fruit is similarly involved remains poorly examined. Health care professionals should be aware of the most recent evidence regarding both grapefruit-drug interactions and its effectiveness in reducing the risk of cardiovascular disease.

MECHANISM OF ACTION

One mechanism of reducing the risk of cardiovascular disease is through an antioxidant effect. Grapefruit has a high antioxidant potential, with red varieties having higher potentials than white.[3] Many different bioactive compounds have been isolated from grapefruit and studied.[1] Grapefruit is high in dietary fiber and several antioxidants, particularly phenolics.[3] Naringin, one of the more abundant phenolics, has demonstrated lipolytic effects in animal and in vitro studies.[4] Another related compound is hesperidin, which showed blood

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pressure reducing activity in vitro.[5] A direct effect on serum lipid levels has been proposed, although evidence to support this is not yet available.

Several compounds called furanocoumarins have been isolated from grapefruit and shown to inhibit enzymes in the liver and intestines.[6] The most important of these are CYP3A enzymes, as these metabolize several drugs in the intestine, reducing their bioavailability. These findings raise concerns that grapefruit interactions may lead to higher plasma concentrations of drugs either enhancing clinical effects or causing adverse reactions. These same compounds also may have anticholesterolemic effects.[7]

CLINICAL STUDIES

Research into the cardioprotective effects of grapefruit developed when a hybrid of the Asian citrus fruit pomelo and grapefruit (called sweetie fruit) was found to significantly reduce total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and triglyceride (TG) levels in hypercholesterolemic patients, though there was no effect on high-density lipoprotein cholesterol (HDL) levels.[8] The peeled fruits were consumed. Animal studies found that grapefruit itself had a cholesterol-lowering effect.[3]

These studies led researchers to test the impact of different grapefruit cultivars in 57 hyperlipidemic patients who had undergone coronary bypass surgery at least 1 year previously and who were unresponsive to statin therapy.[3] The subjects were randomly assigned to eat either one red or one white grapefruit or to a control group. Serum antioxidant activity increased significantly after red and white grapefruit consumption (36.4% and 17.8%, respectively; *P* not reported). In the red grapefruit group, TC, LDL, and TG decreased significantly relative to placebo ($P < 0.0125$, 0.005, 0.005, respectively). With white grapefruit, only LDL values decreased ($P < 0.01$). HDL levels increased in both groups, but not significantly. Weight, blood pressure, and heart rate did not differ between the groups. The absolute change in antioxidant levels was not sufficient to raise concerns such as those elicited by some vitamin E studies.

A randomized, controlled trial (RCT) assigned 91 obese patients to one of four groups taking different fruit or juice ingestion regimens three times daily before meals for 12 weeks.[7] This "preload" consisted of half a fresh grapefruit and a placebo capsule; 8 ounces grapefruit juice with placebo capsule; 7 ounces apple juice with grapefruit extract capsules; or 7 ounces apple juice with placebo capsules. Only the fresh grapefruit group lost significantly more weight than the placebo group (1.6 kg vs 0.3 kg, $P < 0.05$), while the grapefruit juice and grapefruit capsule groups had non-significant weight loss (1.5 kg and 1.1 kg, respectively). None of the groups changed significantly in blood pressure, TG, HDL, insulin, or glucose levels.

Another trial randomized 85 healthy obese adults (body mass index [BMI] 30-39.9 kg/m^2) to consume 127 g of either fresh grapefruit (¼-½ grapefruit), grapefruit juice (4.5 ounces), or water (4.5 ounces) before three daily meals (called the preload phase).[9] Individual meal plans were designed to provide 12.5% fewer calories than expended compared to pre-study consumption. All subjects followed the restricted calorie diet for 2 weeks without consuming grapefruit and then were randomized to one of the groups for 10 weeks. Fresh grapefruit were peeled and consumed without the rind. Average weight loss of 1 kg occurred during the initial 2 weeks and this increased by 13.3% ($P < 0.0001$) during the preload phase. Average overall weight loss was 7.1% of initial body weight. The three groups did not differ significantly in weight loss, body fat composition, blood pressure, glucose, insulin, TC, LDL, or TG levels. Statistically significant increases in HDL levels occurred between the fresh grapefruit group (6.2%, $P = 0.003$) and grapefruit juice group (8.2%, $P = 0.009$) compared to control (3.7% decrease).

The most recent RCT randomly assigned 74 healthy overweight adults (BMI 25-45 kg/m^2) to either a group consuming

Summary Points

- Little evidence is available to support grapefruit's effectiveness in reducing the risk of cardiovascular disease.
- While grapefruit has components that interact with many drugs, including several cardiac drugs, the clinical significance of this is minimal at normal levels of grapefruit ingestion.

half a fresh grapefruit 15 minutes before meals or a control group.[4] The grapefruit was peeled and all portions consumed, including the pith. All participants consumed their usual diet, except that fruit and vegetables containing similar polyphenols to grapefruit were restricted. Everyone was provided a multivitamin, multimineral supplement. The study included a 3-week washout period and a 6-week intervention period. The primary outcome of the study was body weight, with blood pressure, heart rate, and lipid profile (TC, LDL, HDL, TG) being secondary outcomes. Although statistically significant changes from baseline occurred for blood pressure and lipid profiles, these did not differ significantly between groups.

DRUG INTERACTIONS

Concerns about drug interactions arose from an unexpected observation. In a study investigating interactions between a calcium channel blocker (felodipine) and alcohol, grapefruit juice was used to mask the ethanol taste.[10] Drug plasma concentrations were 2-3 times higher than expected.[11] This is now known to be due to furanocoumarins present in grapefruit, which can degrade up to 50% of intestinal CYP3A enzyme. When consumed in usual dietary amounts, grapefruit juice selectively inhibits intestinal CYP3A enzymes and not those found in the liver.[12] The inhibition is persistent, being found to last at least 3 days.[11] However, people vary widely in their levels of CYP3A, leading to much individual variation in the extent of this interaction. Table 1 shows the impact of grapefruit juice on serum levels of several drugs metabolized via these enzymes. However, the practical significance of these interactions continues to be debated, and is likely more significant for juice than whole fruit due to a volume effect.

Several studies have shown that grapefruit significantly changes the serum concentrations of ingested drugs. However, such findings do not necessarily mean that these changes are clinically significant.[12] Many of these drug-monitoring studies involved large volumes or highly concentrated grapefruit juice, leading to calls for studies of "real world" consumption.[12] The first RCT to examine this question was published in 2011, funded by the Florida Department of Citrus. One hundred and thirty patients already receiving atorvastatin (Lipitor, 10, 20, or 40 mg/day) for an extended time were randomized to two protocols. Both groups added 10 ounces pure grapefruit juice daily for 90 days. Group A did not change their dose of atorvastatin, while group B reduced the dose by 50%. After 90 days, serum atorvastatin was 19-26% higher in group A and 12-25% lower in B ($P < 0.01$ between the groups), while TC and LDL were unchanged in A and higher in B ($P < 0.002$ and 0.001, respectively). Body weight, blood pressure, heart rate, TG, and HDL did not differ between the two groups. The actual increases in group B levels were 4% TC, 23% TG, and 9% LDL. Liver and muscle function tests revealed no detrimental changes. The authors concluded that while some changes were statistically significant, they were not clinically significant.[6]

FORMULATION

With recent work identifying furanocoumarins as

Table 1. Area Under the Drug Curve (AUC) Ratio for Grapefruit Juice to No Grapefruit Juice, Representing the Potential of a Drug Interaction with Grapefurit Juice

Drug	AUC ratio*
Atorvastatin	1.33-2.46
Digoxin	1.03-1.09
Felodipine	1.43-2.45
Lovastatin	1.91
Verapamil	1.09
Carbamazepine	1.41
Clozapine	1.01
Cyclosporine	1.23-1.43
Diazepam	3.24
Erythromycin	1.49

*AUC ratio ≥ 5.0 is considered a strong interaction; 2.0 ≤ AUC ratio < 5.0 is moderate; 1.25 ≤ AUC ratio < 2.0 is weak; AUC ratio < 1.25 is negligible.

A much more extensive list is given in Hanley MJ, et al. The effect of grapefruit juice on drug disposition. *Expert Opin Drug Metab Toxicol* 2011;7:267-286.

the CYP3A inhibitors, a method of removing 99% of these from commercial grapefruit juice has been developed.[12] Such juice does not significantly alter the bioavailability of felodipine. Furanocoumarin-free commercial juices are currently being developed.

CONCLUSION

Grapefruit contains numerous phytochemicals that have been found to have a range of biological activities. The fruit, particularly red grapefruit, is high in antioxidants. Although many claims are made about grapefruit's effectiveness in promoting weight loss and reducing the risk of heart disease, recent studies generally have not provided supporting evidence. Only a small number of studies have been conducted in this area, but grapefruit would appear to be a generally healthy fruit rather than having specific therapeutic effects.

Several drug-juice interactions occur, although normal consumption of grapefruit, rather than high volumes of juice, rarely appears to cause clinically significant interactions. Precise volume recommendations are rarely given, though 6-8 ounces per day is sometimes suggested. A complete list of drugs and their susceptibility to this interaction is available.[12]

RECOMMENDATION

Grapefruit is low in calories; high in vitamin C, fiber, and antioxidants; and nutritious. It should be enjoyed as part of a heart-healthy diet and lifestyle. Patients stabilized on medications can consume a fresh grapefruit or a 10-ounce glass of grapefruit juice without fear of major adverse effects. Those taking drugs metabolized by intestinal CYP3A systems and with low oral bioavailability or a narrow therapeutic index should limit their consumption of grapefruit and grapefruit juice. Patients who have had difficulty stabilizing on a suitable dose of such medications should probably avoid grapefruit. People on medications such as those in Table 1 should avoid consuming large amounts of grapefruit. ■

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DIABETES

ABSTRACT AND COMMENTARY

Walnut Consumption and Type 2 Diabetes Risk: The Importance of Associations

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

SYNOPSIS: This large, prospective, cohort trial followed women for 10 years using validated food questionnaires to assess if the consumption of walnuts, other tree nuts, and peanuts was associated with the incidence of the development of type 2 diabetes. The results showed that women who consumed walnuts had a lower incidence of developing type 2 diabetes and that this reduction appeared dose-related though somewhat attenuated when adjusted for body mass index (BMI). The previously described inverse associations between diabetes and total nut or tree nut consumption were essentially negated when adjusted for BMI.[1]

SOURCE: Pan A, et al. Walnut consumption is associated with lower risk of type 2 diabetes in women. *J Nutr* 2013 jn.112.172171.

Given the epidemic of type 2 diabetes confronting the United States and the world, extensive research is focusing on primary prevention. Diet and lifestyle interventions are known to be key components in the prevention of type 2 diabetes with obesity the prime driver of the epidemic. However, evidence in the literature suggests that the composition of the diet, specifically the type of fat consumed, may play a role in the development of diabetes. There is evidence that higher intake of polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) and lower intake of saturated fat and trans fat is associated with a decreased risk of type 2 diabetes.[2]

Prior reports from the Nurses' Health Study (NHS) have shown inverse associations between nut consumption in women and the risk of developing type 2 diabetes but they did not address the issue of specific types of nuts.[3] The current study examined the association between walnuts and the development of type 2 diabetes and compared walnut consumption to consumption of other tree nuts and total nut consumption.

This was a prospective cohort study done as part of the NHS and the Nurses' Health Study II (NHS II) assessing the consumption of walnuts and other nuts and the statistical relationship between consumption of these nuts and the development of type 2 diabetes during the 10-year follow-up period. Because of the known association between diabetes and obesity, analysis also was performed to assess any modulation of effect based on BMI.

The study population previously has been described but briefly consisted of registered nurses with 121,700 participants from 11 states initially enrolled in the NHS in 1976 and an additional 116,671 younger nurses from 14 states beginning in 1989 for the NHS II. This study looked at women aged 52-77 years in the NHS study and aged 35-52 years in the NHS II study each over 10-year periods (NHS 1998-2008 and NHS II 1999-2009). Walnut consumption was included as a variable in the surveys beginning in 1998 (NHS) or 1999 (NHS II), though nut consumption in general had been a part of the surveys beginning in 1986. Exclusion criteria included known diabetes, heart disease, stroke, or cancer at baseline as well as missing information on nut variables, implausible energy intake, or missing information on body weight. This left 58,063 women in the NHS and 79,893 women in the NHS II. The cumulative follow-up of both cohorts exceeds 90% of the potential person-times. Standardized and validated food consumption questionnaires were administered every 4 years. A serving size of 1 ounce or 28 g was used. The diagnosis of diabetes was established by self-reporting of patients confirmed by supplemental questionnaires asking for specific ADA diagnostic criteria. This method had been previously validated within the NHS study.

Summary Points

- Tree nut and peanut consumption are associated with lower rates of development of diabetes, but not when adjusted for body mass index (BMI).
- Walnuts, however, appear to be independently associated with a lower rate of development of type 2 diabetes even when adjusted for BMI.
- Patients may be encouraged to eat nuts, and especially walnuts, in moderation as part of a healthy lifestyle, but should be aware of the caloric density of nuts and the need to maintain a healthy BMI.

There were other covariates assessed and included in the multivariate analysis using time-dependent Cox proportional hazard models including weight, cigarette smoking, physical activity, menopausal status, hormone status, and dietary issues including consumption of alcohol, whole grains, fruits, vegetables, fish, red meat, coffee, and sugar-sweetened beverages. Family history, race, and use of multivitamins were also included in the analysis.

Walnut consumption was inversely associated with the development of type 2 diabetes. Pooled hazard ratios (HRs) (95% confidence intervals [CI]) for participants consuming 1-3 servings/month, 1 serving/week, and > 2 servings/week of walnuts were 0.93 (0.88-0.99), 0.81 (0.70-0.94), and 0.67 (0.54-0.82), respectively, when compared to women who never or rarely consumed walnuts (*P*-trend < 0.0001). Adjustment for updated BMI did slightly attenuate the association, and the HRs (95% CI) were 0.96 (0.90-1.02), 0.87 (0.75-1.01), and 0.76 (0.62-0.94), respectively (*P*-trend = 0.002). The authors did not find any association between walnut consumption and obesity status, physical activity, dietary quality, or family history of diabetes.

When total nut consumption (peanuts, walnuts, and other tree nuts), peanut consumption, and other tree nut consumption (excluding walnuts) were analyzed, there also was an inverse association with the development of diabetes, but this was attenuated to null when adjusted for BMI in all three groups.

COMMENTARY

This study offered convincing evidence for the negative association between walnut consumption and type 2 diabetes at the amounts of intake studied. It is a little puzzling that when walnut consumption was part of the total nut analysis, the results did not support the inverse relationship when adjusted for BMI. It is unclear in the "total nut" or "total tree nut" groups what amount of the nut consumption included walnuts.

The plausibility of the hypothesis that walnuts may confer special health benefits comes from their somewhat unique fatty acid composition. Walnuts are higher in PUFAs (47% by weight) and specifically the omega-3 fatty acid, alpha-linolenic acid (9% by weight). There is substantial evidence for the positive influence of walnut consumption on lipid profiles, markers of endothelial cell function, and markers of the metabolic syndrome.[4,5]

Although the data from this study and others support the inclusion of walnuts as part of a healthful diet, what does this mean in practice? As with all studies that examine the components of diet, it is very difficult to remove other potential confounders. In this study, for instance, it was noted, "women who ate more walnuts also consumed more fish, whole grains, fruit and vegetables, and total energy." They also "were older and tended to weigh less, exercise more, and smoke less than women with infrequent consumption." Additionally, study participants were divided into groups consuming 1-3 servings per month, 1 serving/week, and > 2 servings/week. A serving was defined as 28 g or about 7 walnuts (14 halves).[6] A 28-g serving of walnuts has approximately 185 calories. Although the study showed benefit independent of BMI, these intakes were certainly very modest and there must be some concern about the results of this study encouraging people to increase caloric intake excessively. However, there have been studies showing that people eating unrestricted diets containing nuts had lower BMIs.[4] One weakness was there was not any subanalysis to remove the confounding variables mentioned above.

It should always be cautioned against to attribute cause and effect when looking at cohort dietary studies but it seems reasonable to encourage patients to include modest consumption of walnuts as part of a healthy lifestyle. Walnuts appear to offer greater benefits than do other nuts. Patients should realize that walnuts and all nuts are very calorie dense and that the information we have is limited to the "doses" discussed. For many people, a serving of 7 walnuts two or three times a week would be considered medicinal consumption, not dietary intake! ■

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CANCER

ABSTRACT & COMMENTARY

Qigong Reduces Depression in Women with Breast Cancer Receiving Radiotherapy

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

SYNOPSIS: Ninety-six women with breast cancer undergoing radiotherapy during a 5- to 6-week interval were randomized to either a qigong group or a wait-list control group. The results indicate that the women in the qigong group had clinically significantly less depressive symptoms and better quality of life than the control group.

SOURCE: Chen Z, et al. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: Results of a randomized controlled trial. *Cancer* 2013; Jan 25. doi: 10.1002/cncr.27904. [Epub ahead of print].

A recent study performed at the Fudan University Shanghai Cancer Center in Shangai, China (with collaboration from faculty at the University of Texas MD Anderson Cancer Center in Houston, Texas) identified women with breast cancer (stages 0-III) who had undergone breast surgery and were about to undergo radiotherapy (RT). Ninety-six eligible women participated in this study and were randomized to either a qigong group or a wait-list control (WLC) group. Specific inclusion criteria required that eligible women were 18 years or older; were able to read, write, and speak Mandarin; and were scheduled to receive 5-6 weeks of either inpatient or outpatient RT.

Baseline characteristics of the women were reported to be similar with regard to inpatient vs outpatient treatment, income, type of surgery, and prior chemotherapy. For the outpatient RT group, a form of adaptive randomization called minimization was used to randomly assign the women to either a qigong group or a WLC group. The inpatient RT group was assigned to cohorts to minimize bias. Women were excluded from this study if they self-reported prior regular qigong or tai chi practice in the last year.

The qigong program — a modified version known as "walking qigong" — involved five 40-minute qigong classes, all taught by the same government-licensed traditional Chinese medicine physician and qigong master, each week during the women's 5 or 6 weeks of RT. Additionally, the treatment group was given a DVD and printed qigong materials, and the women were encouraged to practice qigong individually on days when they did not train with the qigong master and after they completed RT. The study reports adherence to the qigong program as high, with 30.4% of women attending 100% of the sessions, 65.2% attending 80% or more of the sessions, and 78.3% of women attending 50% or more of the sessions. Only 13% of women attended less than 20% of the sessions. The WLC group received the standard of care during the study and was offered access to a qigong program after the study ended.

Five major endpoints were assessed in this study via four separate questionnaires (validated and translated into Mandarin) and by saliva samples. Each endpoint was assessed before RT was initiated (T1), in the middle of RT (T2), during the last week of RT (T3), and finally, 1 and 3 months post-RT (T4 and T5). In brief, the endpoints were: symptoms of depression, assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D); fatigue, assessed using the 9-item Brief Fatigue Intervention (BFI); sleep disturbances, assessed via the 18-item Pittsburgh Sleep Quality Index (PSQI); overall quality of life (QOL), evaluated by the 28-item Functional Assessment of Cancer Therapy-General (FACT-G); and cortisol rhythm, evaluated via four saliva samples (waking, 45 minutes later, 8 hours later, and at bedtime) per day for 2 consecutive days.

Summary Points

- Qigong improves depressive symptoms and overall quality of life.
- The positive effects of qigong on patients receiving radiotherapy for breast cancer may be most appreciable after treatment, rather than during treatment.

The main results of the study demonstrate statistically significant differences in changes in symptoms of depression over time for the qigong group but not for the WLC group ($F[3,281] = 2.62$; $P = 0.05$). Of note, both groups did demonstrate that depression scores decreased over time, regardless of intervention.

Interestingly, the results of the study display a consistent theme for all endpoints: the groups with high baseline depressive symptoms displayed a significant difference between treatment and control groups at T4 ($F[1,92] = 13.32$; $P < 0.001$; qigong vs WLC, 15.5 vs 29.1) and T5 ($F[1,90] = 6.48$; $P < 0.005$; qigong vs WLC, 12.74 vs 26.51). Conversely, women with low baseline depressive symptoms showed no significant differences between the qigong and WLC group for any assessment point.

Table: Raw Means of Depression Scores Using the CES-D in Qigong vs Control Groups Over Time

	T1: Baseline		T2: Middle of RT		T3: Last Week of RT		T4: 1 Month Post RT		T5: 3 Months Post RT	
	Qigong	Control	Qigong	Control	Qigong	Control	Qigong	Control	Qigong	Control
CES-D Mean	13.1	12.2	13.1	12.1	12.3	11.6	10.3	11.9	9.5	11.2

With regard to the endpoints of fatigue and overall QOL, significant differences were only appreciated during the later assessments (T4 or T5), and only in the groups who, as mentioned above, presented with high baseline depressive symptoms {Fatigue at T4: ($F[1,90] = 5.36$; $P < 0.05$; qigong vs WLC, 2.93 vs 4.19); overall QOL at T4: ($F[1,90] = 7.71$; $P < 0.01$; qigong vs WLC, 82.44 vs 66.31}. Additionally, with regard to the endpoint of fatigue, controlling for stage at diagnosis demonstrated a significant group × time × baseline depression interaction effect ($F[3,275] = 4.25$; $P = 0.01$). There were no significant differences observed between groups for sleep disturbances or cortisol rhythm.

COMMENTARY

Qigong is pronounced "chee-gung" and translated from Chinese roughly means "cultivating energy."[1] A modern offspring of ancient healing and medical practices in Asia, qigong now exists as one of the pillars of contemporary traditional Chinese medicine.[2] Though there are thousands of variations of qigong practice, this study looked at the form most commonly tested in health research — a blend of generally repetitive flowing movements and postures, a focused state of relaxed calmness, and accompanying breathing techniques.[3]

Stress-reduction techniques, such as meditation, progressive relaxation, guided imagery, yoga, and qigong, are emerging as modalities that may improve QOL and reduce physiological stress in cancer patients.[4] Recent review articles analyzing the effects of qigong have pointed to promising results for patients struggling with depression and psychological well-being.[5,6] Breast cancer patients, specifically, comprise a large population that undergoes significant psychological and physical stress — both from the cancer itself and from side effects of multimodal treatments. Excluding skin cancer, breast cancer is the most diagnosed cancer in women in the United States; in 2012, breast cancer accounted for 29% of all new cancer diagnoses in women (225,870 cases).[7] In 2011, breast cancer was the second leading cause of cancer death in the United States.[8] Thus, the potential for qigong to improve outcomes for women with breast cancer could alter many lives.

It is known that complementary and alternative medical modalities are widely used by breast cancer patients to cope with symptoms of their disease.[9] Although previous clinical trials have demonstrated positive effects of qigong in cancer patients receiving chemotherapy,[10] the authors of this study note that theirs is the first to specifically assess its effect on women undergoing RT. Notably, RT has become more widely used, particularly after a 2011 review demonstrated that RT lowers the chance of breast cancer returning to either breast or lymph node after surgery.[11]

Perhaps the most striking aspect of this study was the stark — and statistically significant — difference in outcomes between women who initially presented with high (vs low) baseline depressive symptoms. As mentioned, the qigong intervention group experienced a reduction in depressive symptoms and improved perceived QOL over time. This result is likely multifactorial. First, and perhaps most evident, is the simple fact that women with worse symptoms have more potential to improve. Second, careful analysis of the data related to both of the study's main outcomes demonstrates that both qigong and WLC groups improved over the course of the 3-month study. This suggests that time itself should also be considered as a healing mechanism, independent of other variables.

Another feature of this study that may have influenced the above outcomes relates to the purported "evenly balanced" qigong and WLC groups. The authors attest that the groups were randomized based on a technique called "minimization" to ensure that groups were similar with regard to age, staging, and type of surgery performed — factors that surely influence emotional and physical response. However, closer examination of the data on women's demographics and clinical characteristics could lead one to conclude that the groups were not as homogenous as the authors claim. With regard to staging, there are a greater number of women with stage III breast cancer in the qigong group vs the WLC group (n = 17 vs 7). Furthermore, fewer women had stage I cancer in the qigong group vs the WLC group (n = 8 vs 14) — recall that stage 0 describes non-invasive cancers that remain within their original location, and stage III describes invasive cancers that have not spread outside the breast to other parts of the body.[12] Therefore, the women in the qigong group may have been predisposed to higher levels of depression at baseline than women in the WLC group, who principally had less invasive cancer diagnoses.

Additionally, this study's analysis and results of cortisol levels was, surprisingly, not statistically or clinically significant, despite the authors' hypothesis that women in the qigong group would demonstrate a steeper diurnal cortisol slope and a smaller cortisol awakening response. Measuring saliva cortisol levels was arguably the most "scientifically precise" assessment method in this study, since, unlike answers to questionnaires, these results could not be compromised by bias, disinterest, or survey-fatigue that might occur after answering 75

questions. The authors of this study assert, and most medical providers would agree, that psychological stress has a considerable impact on cancer patients. Psychological stress, along with the physical stress of surgery and RT, can contribute to hypothalamic-pituitary-adrenal axis dysregulation. Indeed, previous research studying the stress hormone, cortisol, during cancer treatment has shown that cortisol fluctuations may affect tumor progression, overall recovery, and even survival rates.[13] It is unfortunate that no measurable differences in cortisol levels were demonstrated in this study, as perhaps this would be more likely to convince more "Western-minded" medical practitioners and patients that qigong is in fact a validated treatment tool.

As the authors admit, bias and patient expectation were not controlled in this study. Obviously, the individuals in the WLC group knew they were not in the treatment group, and vice versa. An argument against the benefits of any mind-body technique is that the participant must be willing to participate in the technique. With this in mind, contrarily, the women in the qigong group may have anticipated a positive affect from the treatment, therefore potentially influencing their questionnaire responses. Additionally, because this study, and the majority of research examining the effects of qigong takes place in China, its applicability to a more diverse, North American population may be limited. Since qigong originated in China, it would be beneficial to study the effects of non-Western modalities in a more diverse patient population.

Ultimately, the authors of this study admit their findings are "too preliminary" to be able to provide sound clinical recommendations. Indeed, further studies are needed to evaluate endpoints once more time has passed after individuals have completed RT and qigong treatments. Due to the widespread prevalence of breast cancer and the potential for qigong to decrease associated depressive symptoms and improve overall quality of life in patients, it would be worthwhile to perform additional studies. Qigong is generally considered a safe practice, and should be considered among other mind-body techniques as part of an integrated treatment strategy for breast cancer patients. ■

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HEPATITIS C

ABSTRACT & COMMENTARY

Milk Thistle 'Hepato-neutral' for People with Hepatitis C

By David Kiefer, MD

SYNOPSIS: In patients with hepatitis C, having already been treated (unsuccessfully) with interferon, three times daily silymarin in two doses (both supratherapeutic) did not change serum ALT after 24 weeks.

SOURCE: Fried MW, et al. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: A randomized controlled trial. *JAMA* 2012;308:274-282.

For chronic conditions with minimal treatment options, there is always the hope for a new approach that can reverse, or stall, the disease process. Such is the case for people suffering from interferon-resistant hepatitis C (HCV). The researchers of this randomized, controlled trial explored the effect of two high doses of silymarin, the active compound in milk thistle (*Silybum marianum*, Family Asteraceae), as a hepatoprotectant, staving off the damaging effects of chronic hepatitis C infection on hepatocytes and their function.

Inclusion criteria were previous interferon treatment without sustained viral response, measurable serum HCV viral RNA levels, and a serum alanine aminotransferase (ALT) level ≥ 65 U/L. Exclusion criteria included concomitant HIV or hepatitis B infection, pathophysiological changes on liver biopsy, or milk thistle use within the last month.

The researchers randomized 154 study participants into one of three groups, all dosed three times daily for 24 weeks: placebo, 420 mg silymarin, and 700 mg silymarin. The silymarin doses were considered "supratherapeutic," three and five times higher, respectively, than "customary" doses as based on preliminary dose range testing. The milk thistle product used was Legalon 140, a dry extract of milk thistle fruits, commonly used and prescribed in Europe. Each capsule of Legalon 140 is standardized to contain 140 mg silymarin. Therefore, the protocol consisted of five capsules three times daily, either all placebo capsules, three Legalon 140 capsules plus two placebo capsules (420 mg of silymarin per dose), or five Legalon 140 capsules (700 mg per dose).

The primary outcome measurement of interest was a serum ALT < 45 U/L, considered a standard level of interferon efficacy in HCV. The researchers also followed the change in ALT with treatment, serum HCV RNA, adverse events, and quality of life (via the Chronic Liver Disease Questionnaire).

Seventy-one percent of the study participants were men, and 91% had HCV genotype 1 infection. Baseline ALT values for each group were statistically similar (range 105-110 U/L). At the end of 24 weeks, five study participants (one in the placebo group, two in each of the treatment groups) achieved a reduction in ALT to a value below 45 U/L, the primary outcome measure. This improvement was statistically similar across each of the groups. In addition, when the serum ALT was analyzed as a continuous variable over time, again, no difference was noted between any of the groups. Furthermore, no statistically significant difference was noted between groups in quantitative serum HCV RNA or in quality-of-life survey scores over the study period. The trends described above did not change with intention-to-treat analyses, nor when only those 125 patients with > 80% adherence to the study protocol were analyzed separately.

Summary Points

- Twenty-four weeks of silymarin, in two supratherapeutic doses, did not alter serum ALT or HCV RNA in people with interferon-resistant HCV infection.
- The silymarin doses examined were 420 milligrams and 700 milligrams three times daily, whereas most past clinical trials have used 200-480 milligrams once daily.

With respect to adverse effects, the study was likely too small and adverse effects too infrequent to allow accurate detection and conclusions. That said, there was no statistically significant difference in adverse events between placebo and treatment groups (34, 31, and 29, respectively, $P = 0.84$) even though 12% of both silymarin groups reported mild-to-moderate gastrointestinal distress, the most commonly reported adverse event, vs 5% of the placebo group ($P = 0.56$).

COMMENTARY

The authors of this study aptly point out the relevance of their work; citations are provided for the fact that 3% of people suffer from chronic hepatitis C infection, and 33% of those with that infection in the United States take or have taken milk thistle for their condition. It would be nice if those patients were on the right track about the usefulness of this plant for HCV, which is exactly what these researchers strived to corroborate.

Silymarin, a series of four isomeric flavanolignan compounds, should function in this capacity, given what is known about its physiological effects.[1] One proven effect is as an "antitoxic" agent, protecting hepatocytes from insults, possibly by stabilizing the cell membrane; a classic example is the use of silymarin in *Amanita phalloides* mushroom poisoning.[1,2] Silymarin also has antioxidant effects (particularly relevant to one proposed mechanism of HCV-induced liver damage) and prevents glutathione depletion in hepatocytes. Therefore, the in vitro results and proposed clinical effects are in line and relevant.

Addressing inconsistent clinical results in past research, this study used an improved methodology. The authors' aim was to improve on this research backdrop, and it seems as if they did. Prior work had flaws with lack of specific endpoints, a varied study patient population, and non-standardized milk thistle preparations;[3] these issues were addressed specifically in this research protocol. In addition, pharmacokinetic concerns were tackled by their dosing regimen. At first glance, the use of "supratherapeutic" dosing seems to put the researchers out of touch with practical, common clinical use of this botanical medicine. Indeed, most randomized controlled trials of milk thistle in chronic liver disease have used doses of silymarin, or its isomers, from 200-480 mg daily, not the 1260-2100 mg daily used in this study. However, as the researchers point out, milk thistle is rapidly metabolized after an oral dose, its short half-life leading to the need for frequent dosing, or, as in this case, higher individual doses, in order to achieve the best chance of a clinical therapeutic effect. Furthermore, somehow, miraculously, the researchers achieved a high adherence with so many capsules prescribed daily; 95% of the participants met or exceeded a 80% threshold for adherence. It could be argued that this figure is a testament to the researchers' competence in research design and implementation.

Limitations? ALT is an indirect measure of liver health, albeit a much safer intervention than the definitive determination of hepatocyte pathology, a liver biopsy. Changes in hepatocytes may have been occurring with milk thistle treatment, but not appearing in serum ALT. In addition, compounds with a low half-life ideally should be dosed more frequently, not just at a higher dose; it is unclear how the researchers' approach may have improved the chances of milk thistle clinical efficacy. These two minor complaints may or may not have affected the overall outcome.

Should this, or will this, change clinical practice? The demographic studied here is a limited one, so the researchers' results cannot necessarily be applied to patients with other genotypes of HCV, HCV of different severity (interferon-sensitive HCV, for instance), or other types of hepatitis. It appears to be a safe treatment, even in such high doses, so that might sway some clinicians or patients to continue using milk thistle in these cases given the lack of other treatment options. Alternatively, our favorite hepato-protectant may actually just be hepato-neutral for people with interferon-resistant HCV and they may opt to spend their dietary supplement dollars elsewhere. ■

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and;
- 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 INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.

2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Grapefruit is known to contain:

a. antioxidants.
b. vitamin C.
c. phenolics.
d. All of the above

2. The class of compounds that lead to inhibition of intestinal CYP3A enzymes is called:

a. antioxidants.
b. furanocoumarins.
c. phenolics.
d. statins.

3. Drug interactions with grapefruit were first discovered with a(n):

a. antibiotic.
b. beta-blocker.
c. calcium channel blocker.
d. statin.

4. There has been specific focus on walnut consumption as opposed to other tree nuts or total nut consumption because:

a. walnuts have a higher PUFA content, specifically omega 3 fatty acid content, than other nuts.
b. walnuts are lower in calories than other nuts.
c. walnuts have a higher MUFA content (like olive oil).
d. walnuts are higher in protein than other nuts.

5. A recent study on the effects of qigong on women receiving radiotherapy for breast cancer showed that:

a. qigong reduces quality of life.
b. qigong reduces physiological stress via cortisol levels.
c. qigong reduces depressive symptoms during radiotherapy treatment.
d. qigong reduces depressive symptoms after radiotherapy treatment.

6. Which of the following is true regarding the effect of silymarin 420-700 mg three times daily in people with chronic, interferon-resistant hepatitis C?

a. It causes an insignificant rise in serum aspartate aminotransferase.
b. Serum HCV RNA levels drop precipitously.
c. There is no perceptible change in serum alanine aminotransferase when compared to placebo.
d. 700 mg of silymarin three times daily, but not 420 mg three times daily, causes a slight drop in serum alanine aminotransferase.

[IN FUTURE ISSUES]

Medical marijuana

Telomere length and supplements

Supplement use in elderly patients