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CHRONIC DISEASE

Resveratrol: Highlights of Relatively Recent Interest in an Old Chemical

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Dr. Wissink and Dr. Stevens report no financial relationships relevant to this field of study.

SYNOPSIS: Resveratrol has substantial potential to improve health in different ways based on the research. Enough beneficial physiologic responses have been seen in numerous animal models and in limited human studies to warrant long-term human trials studying whether resveratrol supplementation ultimately has a true impact on chronic disease.

Red wine is widely recognized around the world for its cardiovascular benefits, and resveratrol has gained attention as a key ingredient in red wine that looks promising to offer a variety of health benefits. Resveratrol is one of the most biologically active polyphenols in red wine. It has gained progressive interest in the scientific and medical community since 1992, when the "French Paradox" highlighted the potential link between red wine and heart health by reporting that people in France had relatively low incidence of heart disease despite a diet high in saturated fats.[1]

However, long before this in various parts of the world, both red wine and grapes were recognized for their health benefits. It has been reported in various texts that the father of medicine, Hippocrates, recommended wine as a nutritional supplement. The material medica, a collection of traditional Asian medicines and therapeutic foods, described the grape as "good for muscle, bone, and longevity" in its oldest book, estimated to be published in A.D. 22-250.[2]

In addition to grapes and, therefore, wine, resveratrol is also present in various fruits such as cranberry, blueberry, mulberry, lingonberry, bilberry, jackfruit, as well as a number of flowers. Although early resveratrol supplements were extracted from grape skins, now commercially it is extracted from the

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dried roots of *Polygonum cuspidatum* (Japanese knotweed), found mainly in Japan and China. The extract has been used in traditional Japanese and Chinese medicine to treat fungal infections, skin irritation/inflammation, liver disease, and cardiovascular disease.[3]

Over the last 10-15 years, the media has highlighted resveratrol's potential health benefits for both treatment and prevention of multiple age-related diseases. This has led many supplement companies to offer resveratrol-based supplements. These have been so popular that a 2007 study found that resveratrol is taken by two-thirds of people who routinely take supplements.[4]

MECHANISMS OF ACTION

Resveratrol has numerous mechanisms of action that could translate to potential health benefits. Polyphenols in general are recognized for their antioxidant ability. It also induces the expression of a variety of antioxidant enzymes, making it difficult to fully understand precisely how each mechanism contributes to the overall oxidative stress.[5] Resveratrol interacts with a large number of receptors, kinases, and other enzymes that could realistically contribute to health benefits. Many of these influence the regulation of metabolism in multiple body tissues.[6]

Resveratrol has been found to inhibit cyclooxygenases and could, therefore, act through similar mechanisms as aspirin.[7] The cardioprotective mechanism has been postulated to stem from its ability to up-regulate endothethial nitric oxide synthase,[8] which ultimately increases nitric oxide mediated vasodilatation and blood flow.[9] The potential mechanisms of action are so complex that designing human studies to measure specific health outcomes has been difficult thus far.

SIDE EFFECTS AND TOLERANCE

There are no valid data on the toxicity of chronic intake of resveratrol in humans. Based on animal studies, it appears that resveratrol is generally well-tolerated. The longest chronic exposure experiment was 24 months in mice and there were no toxic effects at doses ≥ 1 g/kg body weight per day.[10]

In a double-blind, randomized, placebo-controlled study, healthy volunteers were given 25, 50, 100, or 150 mg of resveratrol six times per day for 2 days (maximum daily dose, 975 mg daily). Adverse effects were mild and similar between the groups.[11] Another small study used daily dosing of 2.5 g or 5 g resveratrol for 28 days. Authors reported that adverse events including gastrointestinal discomfort and diarrhea were mild and reversible.[12]

Resveratrol concentrations in wine vary widely, even within a given variety of grape and growing region. Red wine tends to contain considerably higher amounts than white wine. It is estimated that people who consume one or two glasses of red wine per day get an average of 2-4 mg/day of resveratrol. In supplement form, resveratrol doses are much higher, but also highly variable. Common supplements recommend anywhere from 25 mg to 250 mg per day.

In the clinical studies reviewed, side effects were inconsistent and mild. High doses (> 2500 mg/day) in humans produced frequent abdominal discomfort and diarrhea in participants.

RESEARCH

Several long-term clinical studies are underway but, to date, only small human studies of short duration have been published, and few of these were in peer-reviewed journals. Therefore, the prediction of health benefits has had to rely very heavily on data from animal studies and in vitro studies about potential mechanisms of action. Similarly, a review of the current literature on resveratrol relies heavily on animal studies. In the broad literature search for this review, the most common potential resveratrol health benefits include cardioprotective properties, anti-carcinogenic properties, and prevention of diabetes and obesity. These areas are the focus of this review.

Cardiovascular Effects. Endothelial dysfunction is defined as impairment of endothelial-dependent relaxation, and it is an early event in the development of atherosclerosis and present before structural changes in blood vessels.[13]

Summary Points

- There is evidence to propose that resveratrol reduces the incidence of hypertension, cardiac ischemia, and possibly heart failure in experimental animal models.
- There is evidence to propose that resveratrol improves insulin sensitivity, reduces blood sugar levels, and reduces diet-induced obesity in animal models.
- There is evidence to propose that resveratrol prevents skin cancer in mice and there are also promising results for the prevention of colon cancer in mice as well.
- An optimal and safe dose of resveratrol has yet to be determined for humans, and chronic human intake in the supplement form at doses higher than those found in foods naturally should be considered experimental.

Arterial responsiveness is often measured using flow-mediated vasodilatation (FMD) of the brachial artery. One small study measured FMD 45 minutes after 30 mg, 90 mg, and 270 mg of resveratrol in 19 overweight and obese individuals with unmedicated borderline hypertension. FMD significantly increased compared to placebo at all three dosages.[14]

In one recent review of resveratrol effects in animal studies, nine of 11 studies demonstrated significant reduction in hypertension. On average, the dosing used in the studies was 10 mg/kg/day, which is much higher than with typical wine consumption. The effects were seen within an average of 3 weeks and maintained for 10 weeks. Five other animal studies showed preventive effects of various doses of resveratrol on myocardial infarction induced by surgery in mice/rat models.[15] These studies showed significantly decreased infarct size. Long-term treatment with resveratrol also reduced infarct area after middle cerebral artery occlusion.[16]

Obesity and Diabetes. In 2008, Sirtris pharmaceuticals reported improved glucose tolerance in people with type 2 diabetes treated with resveratrol at a dose of 2.5-5 g/day.[17] In 2010, 10 patients aged 60-80 with impaired glucose tolerance were given resveratrol 1-2 g/day for 4 weeks. Fasting glucose was unchanged, but postprandial glucose levels were lowered without an increase in insulin production.[18] In a 2011 study, 4 weeks of treatment with resveratrol at a much lower dose of 5 mg daily significantly lowered blood glucose levels and delayed peak glucose following a standard meal in 19 people with type 2 diabetes compared to placebo.[19] None of the human studies on clinical effects or bioavailability reported hypoglycemia as a side effect.

Multiple animal studies have found resveratrol to be effective at increasing insulin sensitivity and reducing blood glucose levels. A 2011 review summarized the findings of nine studies using obese or diabetic rats (induced by high-fat diets or genetically and chemically induced diabetes). All nine studies showed reduced insulin levels or increased insulin sensitivity in rats fed 2.5-400 mg/kg/day and covering 1-6 months of treatment.[20] Ten studies looked at the effect on blood glucose levels of genetically obese mice or rats, and all but one study found significantly reduced blood glucose levels following resveratrol exposure for anywhere from 5 days to 2 months.[20] Obviously it is difficult to draw direct conclusions from these studies because of the variability of dosing and duration, but the positive results indicate more long-term human trials are necessary to see if resveratrol is beneficial for obese, diabetic, or prediabetic humans.

Cancer Therapy and Prevention. Resveratrol has been widely publicized as a potential anticancer agent since it was first reported to have an inhibitory effect on the carcinogenic process in 1997.[21] Since then, several animal studies have shown that oral resveratrol significantly reduces the incidence of chemically induced skin cancer in mice, and there have been many in vitro and in vivo animal studies to further evaluate its potential, particularly in the realm of colon cancer and its prevention.

Resveratrol's exact mechanism in chemoprevention appears to be multifaceted. Numerous studies have demonstrated that resveratrol inhibits cellular events associated with all three stages of carcinogenesis, namely, initiation, promotion, and progression.[21,22] As previously discussed, this polyphenol can have similar effects on cyclooxygenase as aspirin and other NSAIDs. This has led to intriguing studies evaluating its effect in the prevention of colon cancer with the theoretical advantage of having a superior cardiovascular profile over NSAIDs. In a 2001 study, oral resveratrol was given to mice that were genetically predisposed to colon cancer. Oral dosing started at 5 weeks of age and continued through senescence. The mice that received the resveratrol had a 70% reduction in tumor formation when compared to the control group.[23]

In vitro and animal studies regarding resveratrol are numerous and promising, and indicate that it has

a good safety profile. However, human trials are scarce. An interesting pilot study carried out in 2009 evaluated the effect of resveratrol on colon cancer in humans. After 14 days of resveratrol in either freeze-dried grape powder or tablets (dose range 20-80 mg depending on the type of tablet), the expression of target genes seen in active colon cancer were not inhibited. However, these same genes existing in normal mucosa showed reduced expression, possibly indicating that resveratrol could have potential in the prevention of colon cancer.[24] It must be noted that this was a small, phase 1 pilot study without dietary control of resveratrol-rich foods that did not account for possible confounders such as medication ingestion.

Challenges with Metabolism and Bioavailability. The numerous and promising in vitro and animal studies are all very encouraging and the results thus far certainly merit further investigation. However, there are challenges when applying polyphenol research results in clinical practice. Resveratrol has been shown to be quickly absorbed but also very quickly metabolized. This occurs primarily via glucuronidation in the liver followed by prompt excretion by the kidneys. In 2004, Walle et al used Carbon-14 labeled resveratrol to better understand its metabolism and found that when given intravenously the plasma concentration rapidly declined over a one-hour period.[25] There is some preliminary evidence suggesting that the metabolites of resveratrol may themselves be bioactive and can be found at much higher concentrations in tissues such as the colon as compared to serum after administration.[26] More work remains to confirm this finding and determine its clinical significance.

CONCLUSION

Resveratrol is an exciting molecule that may have many potential health benefits. There are many intriguing results from animal and in vitro studies but more long-term and well-conducted human studies are necessary. Resveratrol seems safe with limited side effects. In most studies it seems moderate wine consumption, especially red wine, is recommended for cardioprotective effects. Although alcohol possesses cardioprotective properties, it is widely believed that these effects in red wine are related mostly to resveratrol and other polyphenols.

The studies we looked at in both humans and animals used much higher doses of resveratrol than the 2-4 mg/day found in moderate wine consumption. The doses varied widely but were generally 25 mg up to as much as 2500 mg/day. Although some of the effects seen in studies so far are promising, much more research and clinical studies are obviously needed. Many of you will be pleased that at this point we can safely recommend moderate daily red wine consumption for cardioprotective effects based on the studies we reviewed. Chronic human intake above the amount found in natural food should be considered experimental until more long-term human studies have been done. ■

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BONE HEALTH

Vitamin D Supplementation and Bone Mineral Density: Is There an Effect?

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

SYNOPSIS: This systematic review and meta-analysis investigated the effects of vitamin D supplementation on bone mineral density (BMD) and found no significant effect of vitamin D supplementation on the hip or spine and a small and significant increase in femoral neck BMD.

SOURCE: Reid R, et al. Effects of vitamin D supplements on bone mineral density: A systematic review and meta-analysis. *Lancet* 2014;383:146-155 [Epub 2013 Oct 11].

The authors set out to examine whether vitamin D supplementation without calcium affects bone mineral density (BMD), as the relationship between vitamin D and BMD is not well defined.[1] Using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines and a predetermined protocol to perform their review, the authors determined that inclusion criteria were:

- Randomized, controlled trials
- Study populations with an average adult age > 20 years
- Study interventions that only varied in supplementation with vitamin D, and supplementation with vitamin D3 or D2 but not a vitamin D metabolite
- Any other interventions were required to be equally distributed across all groups
- Studies that included BMD data and bone mineral content
- Studies were excluded that had patient populations with disorders that were likely to affect calcium or bone metabolism

The search criteria to identify potential studies was performed using the search engines Web of Science, Embase, and the Cochrane database up to July 8, 2012. The authors used the search terms "vitamin D," "c(h)olecalciferol," or "ergocalciferol," together with either "randomized study" or "randomized trial" or "controlled clinical trial." The reference lists of reviews of vitamin D also were screened for qualifying studies. To perform the statistical analysis, the authors used the percentage of change in BMD as the primary endpoint that was investigated.

Summary Points

- The results of this meta-analysis are most relevant to a white female population of approximately 59 years of age.
- No significant effect of vitamin D supplementation on bone mineral density (BMD) in the hip or spine was demonstrated.
- A small and significant increase in femoral neck BMD with vitamin D supplementation was demonstrated.
- The mechanism of action of vitamin D alone in bone mineralization has not been fully elucidated and is still actively being investigated.
- For preventing hip fractures in the elderly population, 1200 mg of calcium per day and 800 IU of vitamin D are effective doses.

The authors pooled the data with a random effects meta-analysis model and reported weighted mean differences and 95% confidence intervals (CI). To investigate the effects of vitamin D on BMD, the authors compared the data between the subgroups of trials, which were defined by prespecificed characteristics. The subgroup examples cited in the study were baseline age, vitamin D status, treatment dose, and trial duration. All statistical tests were two-tailed and a P value < 0.05 was considered to be statistically significant. To assess the level of

Table 1. Vitamin D Conversion Table between ng/mL to nmol/L

Vitamin D Status	ng/mL	nmol/L
Deficient	< 12	< 30
Insufficient	12-20	30-50
Sufficient	≥ 20	≥ 50

1 nmol/L = 0.4 ng/mL
Source: NIH: http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

Table 2. Baseline Mean 25(OH)D Measurement

Number of Studies	Baseline 25(OH)D Measurement	25(OH)D ng/mL
3	Not measured	
5 (n = 1181)	< 30 nmol/L	< 12 ng/mL
3 (n = 610)	30-50 nmol/L	12-20 ng/mL
11(n = 1860)	50-75 nmol/L	> 30 ng/mL
1(n = 187)	> 75 nmol/L	> 30 ng/mL

heterogeneity in individual studies, the Cochran's Q statistic and the I^2 statistic were calculated with the $I^2 > 50\%$ used as the threshold for significant heterogeneity. Funnel plots and Egger's regression model were used to assess any publication bias.

They identified 3930 unique publications that were considered for inclusion in the study. Fifty-four articles were retrieved, and 23 met the inclusion criteria and were included in the analysis. In the 23 studies analyzed, 4082 participants (92% women) were included. The mean weighted age for all 23 studies was 59 years old, and in six studies (with a total of 871 participants), the average age was < 50 years. The ethnicity of the participants was predominately white in 19 studies; two studies included were done exclusively in African American individuals, one in a Bangladeshi population, and one in Pakistani immigrants in Denmark. Two of the studies were in overweight populations.

25-hydroxyvitamin D Measurement. In 19 studies, 25-hydroxyvitamin D (25(OH)D) was measured at baseline in all individuals (*see Tables 1 and 2*). In one study, only 15% of participants had 25(OH) D values; it was not measured in three studies. The mean 25(OH)D was < 30 nmol/L (< 12 ng/mL) in five studies (n = 1181), 30-50 nmol/L (12-20 ng/mL) in three studies (n = 610), 50-75 nmol/L (20-30 ng/mL) in 11 studies (n = 1860), and > 75 nmol/L (30 ng/mL) in one study, the latter in 187 healthy Australian women in early postmenopause (*see Tables 1 and 2*). The unweighted mean vitamin D ranged from 53 nmol/L to 92 nmol/L, and no CI was reported.

Table 3. Type of Vitamin D Supplementation

Number of Studies	Vitamin D Supplementation
18	Vitamin D3
5	Vitamin D2
1	Vitamin D*

* The type of vitamin D is unknown to the reviewer as it is not clearly stated in the meta-analysis nor is it stated in the actual abstract of Venkatachalam S. et al.[2] However the dose is consistent with a vitamin D2 IM injection.

Trial Characteristics. A number of different dosing regimens, including daily, weekly, and monthly oral and annual intramuscular injections, were noted in the individual studies and assessed. Daily average dosing was ≤ 500 IU in six studies (n = 1648), 500-799 IU in four studies (n = 646), and ≥ 800 IU in 13 studies (n = 1788) (*see Table 3*).[2] The trial durations were also variable and ranged from 6 months to 5 years. The weighted mean trial duration was 23.5 months. In 12 studies, calcium was given to all trial groups. In two studies (n = 243), the participants had average total calcium intakes of < 750 mg per day. One study used a crossover design, whereas all others were parallel group study.

BMD. BMD was measured between one to five sites (lumbar spine, femoral neck, total hip, trochanter, total body, or forearm) in the included studies. The hip was assessed in 12 studies and the trochanter in three studies. The authors combined the hip and trochanter data in the meta-analysis. No significant effect of vitamin D on BMD was found in the spine, combined hip analyses, total body, or forearm.

Six studies showed beneficial effects on BMD in this meta-analysis from five primary studies out of the 23 total studies (*see Table 4*).[3-7] Four of the five studies reported positive effects at one site only and one study reported beneficial effects in both femoral regions (*see Table 4*).

Of the five studies with positive outcomes, three reported baseline 25(OH)D levels between 26-36 nmol/L. In the other two positive studies, 25 (OH)D levels in the control groups were 66 and 71 nmol/L

Table 4. Characteristics of Positive Studies

Authors	Baseline Vitamin D	Intervention	Results Weighted Mean Difference BMD (%) (95% CI)
Dawson-Hughes et al, 1991[3]	71 nmol/L	vitamin D3 400 IU/day vs placebo x 12 months	Lumbar spine 0.7 (0.0-14)
Dawson-Hughes et al, 1995[4]	66 ± 25 nmol/L	vitamin D3 100 IU/day vs 700 IU/day x 24 months	Femoral neck 1.5 (0.5-2.5)
Ooms et al, 1995[5]	26 nmol/L range (19-37)	vitamin D3 400 IU/day vs placebo x 24 months	Femoral neck 1.9 (0.4-3.4)
Islam et al, 2010[6]	36 nmol/L	vitamin D3 400 IU/day vs placebo x 12 months	Femoral neck 2.8 (1.5-4.1) Hip/Trochanter 3.0 (1.2-4.8)
Harwood et al, 2004[7]	29 nmol/L range (10-67)	vitamin D2 300,000 IU/year IM vs no treatment x 12 months	Hip/Trochanter 2.0 (0.5-3.5)

(*see Table 4*). The authors also note that the five positive studies had varying treatment times from 12 months to 24 months. These findings suggest that the baseline 25(OH)D levels and the treatment duration were not factors in the positive outcomes. All of the positive studies were in women; four were in older white women and one was in Bangladeshi women. The author's state, "that there was no suggestion of ethnic differences in response demonstrated."

Overall Results. No significant effect of vitamin D supplementation on BMD in the hip or spine was demonstrated.

A small and significant increase (0.8 % in femoral neck BMD; 95% CI, 0.2-1.4; $P = 0.005$) in femoral neck BMD with vitamin D supplementation was demonstrated. However, the authors state "Such a localized effect could be artifactual or could be a chance finding" and that there was evidence of heterogeneity in the studies ($I^2 = 67\%$, $P = 0.00027$).

No significant interactions were found with age, number of participants, sex, study duration, 25(OH) D concentration, vitamin D dose, baseline BMD, or type of DXA machine with meta-regression analysis on the femoral neck BMD effect.

Two studies reported a decreased total-body BMD ($P \leq 0.05$) with vitamin D supplementation. The results of the meta-analysis on the eight studies with the total body BMD data did not show a significant effect of vitamin D supplementation on total body BMD in either direction.

■ COMMENTARY

The question of whether vitamin D affects BMD is an important question that is applicable to clinicians and patients. The conclusion of this meta-analysis is somewhat surprising, as the investigating authors suggest that vitamin D supplementation to prevent osteoporosis in healthy community-dwelling adults is not indicated. This conclusion is in opposition to recent research studies and the U.S. Institute of Medicine (IOM) recommendation that elderly adults should have an intake of 1200 mg of calcium and 800 IU of vitamin D per day for skeletal health.[8-10]

Although the conclusion is surprising, the authors' search survey appears to be quite exhaustive. The authors performed the meta-analysis with PRISM guidelines and predetermined protocols. Altogether, the study methodology and results appear to be sound. However, the question of whether vitamin D supplementation affecting BMD is best addressed by a meta-analysis study design is an important one. The benefits of a meta-analysis are the increased statistical power of the study and the increased number of participants; however, there are a number of drawbacks. The effects that vitamin D has on the body and, specifically BMD, are seemingly more complicated than previously understood.

The vitamin D dosing among the included studies was quite variable as was the duration of the trials. In addition, the interaction with calcium supplementation would be incompletely addressed in a format focused on vitamin D supplementation alone. As more information is being ascertained regarding the complexities of the vitamin D pathway,

there are many known and unknown factors, such as genetic variation, that were not factored into the individual studies of the meta-analysis and their effects cannot be measured.

The IOM recommendation that elderly adults should have an intake of 1200 mg of calcium and 800 IU of vitamin D per day for skeletal health is further corroborated by other research studies that have larger numbers of participants than the Reid et al study.[8-10] Two other studies that have further supported the IOM recommendation are the vitamin D individual Patient Analysis of Randomized Trials (DIPART) group and the Bischoff-Ferrari and colleagues study.[8-10]

Abrahamsen and colleagues of the DIPART group concluded that vitamin D supplementation of 10-20 mcg without calcium is not effective in preventing fractures. However, Abrahamsen et al concluded that "calcium and vitamin D given together reduce hip fractures and total fractures, and probably vertebral fractures, irrespective of age, sex, or previous fractures" in the DIPART study, which included 68,500 patients from trials in the United States and Europe.[9]

Bischoff-Ferrari and colleagues also concluded that "high-dose vitamin D supplementation (≥ 800 IU per day) may reduce the risk of hip fracture in persons 65 years of age or older, independently of type of dwelling, age, and sex."[10] The Bischoff-Ferrari study included 31,022 patients from 11 double-blind RCTs and also concluded that a 25(OH)D level > 60 nmol/L is optimal to prevent fractures.[10]

Until the complexities of the vitamin D pathway are further studied and the exact mechanisms of actions of its role in bone mineralization are elucidated, the IOM recommendation of 1200 mg of calcium and 800 IU of vitamin D per day for skeletal health is well substantiated and an effective approach to prevent hip fractures.[8-11] ■

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WOMEN'S HEALTH

ABSTRACT & COMMENTARY

The Effect of Yoga, Exercise, and Omega-3s on Menopausal Symptoms

By Melissa Quick, DO, and David Kiefer, MD

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

SYNOPSIS: This 12-week, randomized, controlled trial assessed the effect of yoga, exercise, and omega-3 supplements on menopausal symptoms in 355 women. Yoga slightly improved quality of life, whereas exercise and omega-3s did not.

SOURCE: Reed SD, et al. Menopausal quality of life: RCT of yoga, exercise and omega-3 supplements. *Am J Obstet Gynecol* 2013; doi: 10.1016/j.ajog.2013.11.016 [Epub ahead of print].

This study examined the effect of three common non-hormonal supplements — yoga, exercise, and omega-3 fatty acids (omega-3s) — on the vasomotor symptoms (VMS) associated with menopause. The study enrolled 355 eligible women (aged 40-62 who were perimenopausal

or postmenopausal) in a multisite, 3 × 2 factorial randomized, controlled trial. The women were randomized to 12 weeks of yoga, exercise, or usual activity. Concurrently, the group of 355 women was also randomized to take 1.8 g/day of omega-3 or placebo capsules.

The yoga component consisted of both studio and home practice techniques including breathing exercises, 13 poses, and guided meditation. Instruction included 12 weekly, 90-minute classes, and daily home practice was expected to be completed for 20 minutes on days without classes. The exercise arm included 12 weeks of three individual cardiovascular conditioning training sessions per week at local fitness facilities, supervised by trained and certified exercise trainers. The usual activity group was asked to maintain current exercise practices and to not begin a new yoga or new exercise regimen during the study.

The omega-3 supplement contained 425 mg ethyl eicosapentaeonic acid (EPA), 100 mg docosahexaenoic acid (DHA), and 90 mg of other omega-3s. The placebo capsule contained olive oil.

The main outcome of the study was to assess quality of life (QOL). A 29-item evaluation known as MENQOL (Menopause Quality of Life) assessed women's outcomes at baseline and at week 12. The MENQOL focused on four main domains: vasomotor, physical, psychosocial, and sexual functioning. Each scored item received a "1" for non-endorsement or a "2" for endorsement of symptoms, and also a "bother score" ranging from 0 to 6 (0 indicating the symptom was not bothersome and 6 indicating the woman was extremely bothered) for a maximum score of 8.

With regard to VMS, the frequency and severity of the symptoms were recorded retrospectively on daily diaries in the morning for night sweats and in the evening for daytime hot flashes. Additional validated menopause QOL measures included the Hot Flash-Related Daily Interference Scale (HFRDIS); Perceived Stress Scale (PSS); Pain Intensity, Interference with Enjoyment of Life, and Interference with General Activity scale (PEG); and Female Sexual Function Index (FSFI), collected at baseline and 12-weeks.

Other outcomes of the study — insomnia, subjective sleep quality, depressive symptoms, and anxiety — were gauged using several other questionnaires.

Of the 355 randomized women, 338 (95%) completed 12-week assessments. The mean baseline VMS frequency was 7.6/day and the mean baseline MENQOL score was 3.8 (ranging from 1, indicating "better," to 8, indicating "worse"). There was a modest yet significant improvement in the total MENQOL for the yoga cohort: -0.3 (95% confidence interval [CI], -0.6 to 0.0; $P = 0.02$). An additional statistically significant difference in MENQOL domain scores favoring the yoga intervention was observed in the sexual domain (-0.5; 95% CI, -1.0 to 0.0; $P = 0.03$).

Summary Points

- Twelve weeks of a combination of home and studio yoga improved scores, albeit modestly, on a menopausal quality-of-life scale in perimenopausal women.
- Twelve weeks of exercise improved the physical component of the menopausal scale, but omega-3 supplementation had no effect on overall menopausal symptoms or on sub-components.

For the exercise and omega-3 cohorts, there was only one statistically significant treatment difference: The MENQOL score for physical symptoms improved with exercise intervention (-0.2; 95% CI, -0.5 to 0.0; $P = 0.02$). There was no domain score difference between the omega-3 and placebo groups.

■ COMMENTARY

Approximately 80% of all women experience perimenopausal symptoms, ranging from mild to severe.[1] Common perimenopausal symptoms include mood changes, bloating, headaches, hot flashes, night sweats, tiredness, insomnia, weight gain, depression, irritability, vaginal atrophy, and dyspareunia.

More than 88% of U.S. women experience VMS (primarily daytime hot flashes and night sweats) as they transition into menopause.[2] In general, the overall duration of hot flashes tends to range from 6 months to 2 years.[3] VMS are among the most common reasons for clinical visits for mid-life women and, subsequently, increases health care expenditures.[4] As such, physicians must be poised to counsel women on a variety of treatment modalities, ranging from hormonal therapy (HT) to effective nonhormonal modalities.

In the past, HT was commonly prescribed to treat menopausal symptoms. Indeed, current evidence demonstrates estrogen therapy is the most effective treatment of menopause-related VMS.[5] However, despite estrogen's efficacy on reducing VMS, concerns regarding the side effects of HT have

reduced the prescription duration for hormones and, perhaps more importantly, have raised women's awareness to seek alternative treatments for their symptoms. An additional option during menopause counseling that may ease women's concerns is to emphasize that menopause is a natural transition, not a disease state. This may help reframe the idea for women and perhaps ease the transformation.

The evaluation of the QOL of women experiencing menopause may be one of the best ways to determine just how bothersome symptoms are. Correspondingly, if QOL is evaluated both before and after a given intervention, such as in the study reviewed above, this might provide the best evidence of efficacy for a treatment. Remarkably, there are no hormone therapy products with government approval specifically for the improvement of QOL in menopausal women.[6] Additionally, a literature review reveals there are limited studies evaluating menopause-related QOL in menopausal women.

Physical activity has been advocated for the management of mild-to-moderate menopausal symptoms in the past.[3] Interestingly, a high body mass index is associated with an increased prevalence of VMS.[5] As such, it is reasonable to ascertain that an alternative modality that encourages physical activity and that can lead to weight loss — exercise or yoga — may have beneficial effects on decreasing VMS and other menopausal symptoms.

In this study, exercise *did* improve scores in the "physical function domain" of the MENQOL (-0.2; 95% CI, -0.5 to 0.0; $P = 0.02$) when compared to usual activity, but did *not* affect overall menopause-related QOL. The yoga cohort, conversely, *did* demonstrate an improvement, albeit small, in VMS. As mentioned above, statistically significant differences in MENQOL domain scores favoring the yoga intervention were observed for the "vasomotor domain" (-0.3; 95% CI, -0.8 to 0.2; $P = 0.02$) and "sexual domains" (-0.5; 95% CI, -1.0 to 0.0; $P = 0.03$).

Yoga is gaining popularity in the CAM world for multiple ailments and has been shown to reduce fatigue, blood pressure, and anxiety.[7] Previous literature reviews indicate that yoga may have a more pronounced effect on the psychological aspects of menopause, rather than somatic vasomotor symptoms.[7] While the exact beneficial mechanism of yoga is unknown, it is postulated that yoga may normalize the psychological state by controlling counter regulatory hormones. Additionally, yoga may create a hypothermic state and could alter the sympathetic/parasympathetic nervous system[1] — one explanation for possible improvement of VMS with this technique.

In this study, omega-3 supplementation did not improve QOL or decrease VMS in menopausal women. While some data exist for the benefit of omega-3s for cardiovascular disease, rheumatoid arthritis, and depression, current data are incomplete and inconsistent for any benefit on VMS.[8] If the women who were randomized to take omega-3 supplements took the capsules three times a day, as instructed, they would have received a total daily dose of 1.845 g (1.575 g of EPA plus DHA) of fish oil daily. This is within the scope of commonly prescribed doses of fish oil: Clinically studied doses range from 1-4 g of EPA plus DHA daily for cardiovascular disease, hypertriglyceridemia, and hypertension.[9]

In conclusion, providers should be familiar with common menopausal symptoms and be prepared to offer mid-life women a variety of options in which to alleviate their discomfort. This study represents another step in our exploration of safe, alternative modalities to treat menopausal symptoms. While we continue to research the efficacy of yoga and other alternative modalities, we should emphasize to women that although menopause can be uncomfortable, it can also be a time for personal growth and new perspective. Based on the results of this study, it is reasonable to recommend yoga as a low-cost, non-invasive technique to alleviate discomfort associated with this life transition. Moreover, given the potential benefits of yoga discussed above, providers should present yoga as a healthy option to menopausal patients not just for perimenopausal symptoms, but for their general health as well. ■

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DEPRESSION

SHORT REPORT

Curcumin Comparable to Fluoxetine for Treatment of Major Depressive Disorder

By Carrie Decker, ND

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

SYNOPSIS: A randomized, controlled trial of curcumin, fluoxetine, or fluoxetine with curcumin for treatment of major depressive disorder finds comparable improvement in depression score in each treatment group.

SOURCE: Sanmukhani J, et al. Efficacy and safety of curcumin in major depressive disorder: A randomized controlled trial. *Phytother Res* 2013; Jul 6 [Epub ahead of print].

Curcumin, the primary active constituent of *Curcuma longa*, is well known for its antioxidative and anti-inflammatory actions, but also has been used traditionally for conditions including depression and anxiety in Chinese and Ayurvedic medicine. Animal studies have shown curcumin to have an antidepressive effect by promoting neurogenesies in the hippocampus as well as acting as a monoamine oxidase inhibitor. This study is the first known clinical trial of curcumin for the treatment of major depressive disorder (MDD).

Sixty individuals diagnosed with MDD (not having other psychiatric disorders or other uncontrolled organic disease) were randomized to treatments with 20 mg of fluoxetine, 1000 mg of curcumin (500 mg twice daily), or these treatments in combination for a period of 6 weeks. There was not a placebo group. The study was observer-masked but participants were not blinded to their treatment regimen. Efficacy of treatment was measured by the Hamilton Depression Rating Scale, 17-item version (HAM-D17). Forty-five individuals completed the study, with no significant difference in each group. The mean change in HAM-D17 score was comparable in all three groups ($P = 0.77$) with a mean change of -14.0 in the fluoxetine group, -12.6 in the curcumin group, and -14.8 in the combination group. A slightly lower tolerability was found in the combination treatment group, but the difference was not significant, with only mild side effects reported. ■

Summary Point

- Curcumin may be an effective alternative or adjunctive treatment for major depressive disorder.

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. Scan the QR code to the right or 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.

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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 QUESTIONS

1. Which of the following are limitations so far in the study of resveratrol?
a. Very few human clinical trials have been completed.
b. There is a wide range of dosing used in the animal studies.
c. The mechanisms of action of resveratrol are complex which makes measurement of specific health outcomes difficult.
d. All of the above.

2. Resveratrol is most well-known for which of the following potential health benefits?
a. Prevention of autoimmune disease
b. Prevention of Alzheimer's disease
c. Cardioprotective effects
d. Increased athletic performance

3. Which of the following is true about resveratrol?
a. It is metabolized very slowly once absorbed.
b. Most of the studies so far have focused on potential cardioprotective effects, possible prevention and treatment of cancer, and benefits for diabetes/obesity.
c. It is found at higher concentrations in white wine rather than red wine.
d. Grapes are the only known source of resveratrol.

4. Which of the following is true about vitamin D supplementation?
a. It does not increase bone mineral density.
b. It may increase bone mineral density at the femoral neck.
c. It significantly increased bone mineral density at the spine and hip.
d. It decreased bone mineral density at the femoral neck.

5. Which is the most effective non-hormonal treatment modality for vasomotor symptoms associated with menopause?
a. Omega 3 fatty acid supplementation
b. Exercise
c. Yoga
d. Meditation
e. Hypnosis

6. Curcumin, dosed at 500 mg, twice daily:
a. is well tolerated and may improve symptoms of major depressive disorder.
b. is poorly tolerated but may improve symptoms of major depressive disorder.
c. is poorly tolerated and does not improve symptoms of major depressive disorder.
d. is well tolerated but does not improve symptoms of major depressive disorder.

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[IN FUTURE ISSUES]

Fermented milk and brain health

Multivitamins and cognitive function

Anthocyanin intake and MI in women