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Creatine, Conjugated Linoleic Acid, and Resistance Training

By Dónal P. O'Mathúna, PhD

Dr. O'Mathuna is a lecturer in Health Care Ethics, School of Nursing, Dublin City University, Ireland; he reports no financial relationships relevant to this field of study.

WITH THE RECOGNITION THAT EXERCISE MUST BE PART OF ANY weight loss program, some attention has been given to the optimal role of dietary supplements. One suggestion has been that certain supplements may support the beneficial changes in body composition that accompany resistance exercise. People who are overweight will benefit not only from losing weight, but also from reducing the proportion of fat in their bodies and increasing their fat-free mass (FFM). Exercise can use up some of the fat stored in the body and increase muscle mass and strength. This has led to interest in whether certain supplements stimulate similar changes in body composition. The combined administration of two such supplements, creatine and conjugated linoleic acid (CLA), along with resistance training, recently produced intriguing results among older adults.[1]

Background

Creatine has been a very popular supplement among athletes.[2] Much evidence supports claims that creatine enhances power output during short maximal bursts of exercise, such as power lifting or sprinting.[3] The benefit is noted particularly when the bursts are repeated intermittently in what is called interval training. These outcomes have led to interest in using creatine to promote development of muscle and FFM. Aging is associated with reduced muscle mass and strength, which can lead to functional impairment and reduced quality of life. Sarcopenia refers to the condition when fat free mass is more than 2 standard deviations below normal.[1] Resistance training is also suggested for age- and disease-related loss of muscle mass, strength, and function.[4] Numerous studies have demonstrated that resistance exercise counteracts sarcopenia, leading to investigation of complementary strategies to supplement those gains. Exercise with supplementation might be preferable to

exercise alone or other invasive or pharmacological alternatives.

CLA has received less research than creatine as a dietary supplement. Interest in CLA developed after a number of animal studies showed a reduction in body fat when the animals consumed CLA, regardless of their quantity or type of fat intake.[5] This has led to some research into its use as a supplement that might generate favorable changes in body composition in humans.

Pharmacology

Creatine is made from three amino acids common to protein. On average, people require about 2 g of creatine daily, obtained equally from exogenous and endogenous sources.[6] Humans store 95% of their creatine in skeletal muscle, with more found in fast twitch muscle fibers than slow twitch ones.[7] Creatine is essential to allow regeneration of muscles' biochemical energy levels so that intense exercise can be sustained.

CLA is a group of very closely related natural chemicals belonging to the omega-6 fatty acids.[5] Supplements usually contain a mixture of these fatty acids, although two tend to predominate. CLA occurs naturally in dairy products, beef fat, and some plant oils.[1] However, the amount of CLA in milk, for example, varies enormously depending on the cows' diet (grazing or feed) and time of the year (highest when cows graze on rapidly growing grass).[5] Such background variability complicates attempts to study the impact of CLA on body composition. Studies of creatine and CLA combinations are further complicated by large variability found in individual responses to creatine supplementation.

Clinical Studies

The first study examining creatine and CLA supplementation with resistance training involved 39 community-dwelling, healthy adults (aged 65-85 years).[1] Participants were randomized to receive either creatine (5 g/day) with CLA (6 g/day) or placebo for 6 months. No participants had engaged in an exercise program during the previous 2 years, and all participated in supervised resistance training twice a week for the duration of the study. All measures of strength increased for both groups. Isokinetic (resistance at a constant speed) strength increased significantly more in the supplement group ($P < 0.05$), but isometric (performed at static position) strength gains did not differ between the groups. The supplement group had significantly better increases in FFM and decreases in total fat mass ($P < 0.05$).

Use of CLA has been promoted on the basis of animal studies showing that CLA supplementation led to reduced weight gain. However, other animal studies have shown no effects from CLA supplements.[8] Where effects did occur, they were dependent upon the amount and type of compounds present in the CLA mixture. The results of trials in humans have been inconsistent, with no dose response effect and a smaller effect size than seen with animals. A study with twenty healthy adults, who exercised for 90 minutes three times a week in the gym, found significant reductions in body fat with CLA compared to placebo.[9] However, differences in body weight were not found between the two groups. In another study, 17 healthy women (aged 20-41 years) were randomly assigned to receive either CLA or placebo.[10] They lived in a controlled metabolic unit for 94 days. No significant differences were found between the groups for changes in body weight, fat mass, FFM, or percentage body fat. Energy expenditure and respiratory parameters did not vary between the groups either at rest or when walking. Similar non-significant results were found for CLA supplementation in experienced resistance-training men (mean age 23 years).[11]

The use of creatine supplements with resistance training among older, non-athletes dates back from the late 1990s.[12] Thirty-two men and women (67-80-years-old) were randomized into four groups: creatine with resistance training, placebo with training, creatine without training, and placebo without training. None of the participants did weight-lifting before the study, and all were

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Table 1

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) refers to a family of many isomers of linoleic acid (at least 13 are reported), which are found primarily in the meat and dairy products of ruminants. As implied by the name, the double bonds of CLAs are conjugated.

Biochemistry

Conjugated linoleic acid is a trans fat, though some researchers claim that it is not harmful in the same fashion as other trans fatty acids, but rather is beneficial. CLA is a conjugated system, and in the United States, trans linkages in a conjugated system are not counted as trans fat for the purposes of nutritional regulations and labeling. CLA, as well as some trans isomers of oleic acid, is produced by microorganisms in the rumen of ruminants. Non-ruminants, such as humans, are able to produce some isomers of CLA from some trans isomers of oleic acid, such as vaccenic acid, which is converted to CLA by delta-9-desaturase.[1,2]

Diet and health

Studies on CLA in humans shows a tendency for reduced body fat[3] particularly abdominal fat, changes in serum total lipids and decreased whole body glucose uptake. The maximum reduction in body fat mass was achieved with a 3.4 g daily dose.[4] CLA supplementation has, however, been shown to increase C-reactive protein levels and to induce oxidative stress[5] and to reduce insulin sensitivity and increase lipid peroxidation.[6]

Possible side effects of CLA in humans

There are concerns that the use of CLA by overweight people may actually cause insulin resistance, leading to an increased risk for developing diabetes.[7,8]

Dietary Sources

Kangaroo meat may have the highest concentration of CLA when compared with other foods.[9] Food products of grass-fed ruminants (e.g. lamb, beef) are good sources, and contain much more CLA than those from grain-fed animals.[10] In fact, products of grass fed animals can produce 300-500% more CLA than cows fed the typical diet of 50% hay and silage, with 50% grain.[11]

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Source:

http://en.wikipedia.org/wiki/conjugated_linoleic_acid

Accessed December 10, 2007.

sedentary-to-moderately active. Creatine dose was 20 g/day for 5 days, followed by 3 g/day for a total of 8 weeks. Resistance training was carried out 3 times a week. No significant changes in body mass or body fat were found in any group. Training groups had significantly increased strength and endurance compared to those not training. Creatine supplementation did not provide any additional benefit.

A double-blind, randomized trial assigned 30 men (mean age 70 years) to receive either creatine (0.3 g/kg for 5 days, followed by 0.07 g/kg daily) or placebo.[13] Both groups engaged in three sessions of resistance training per week for 12 weeks. Both groups had significantly increased FFM, with the increase being significantly greater in the creatine group ($P < 0.05$). Fat mass did not differ between the two groups. With two of the three muscle groups trained, the creatine group had significantly greater improvements in strength and endurance. The training volume was 31% higher in the creatine group ($P = 0.05$). Training volume is a measure of the total amount of exercise calculated from the total weight used and the total number of repetitions.

Adverse Effects

Creatine frequently leads to a weight gain of 1-3 kg, probably due to intramuscular water retention.[14] Numerous anecdotal reports from athletes claim creatine supplementation causes gastrointestinal problems, muscle cramping, and renal problems. One study with older men found significantly more reports of loose stools during creatine loading than with placebo.[13] Also, after 3-5 weeks, muscle cramping and strains were more frequent with creatine than placebo. Whether creatine adversely affects renal function remains controversial and unclear, suggesting that those at high risk for renal disease should be monitored medically.[15]

CLA has similarly been reported to cause gastrointestinal problems. However, the impact of CLA on insulin resistance is of more concern. While commentators on the animal studies have focused on CLA's beneficial effects, recorded adverse effects have been largely ignored.[8] Numerous animal studies have found that CLA induces insulin resistance and, thus, should be avoided by anyone at risk of diabetes. Animal studies have also found enlargements in the liver and spleen. However, little is known about the actual risks from CLA supplementation in humans.

Formulation

Creatine is readily available from meat and fish (containing roughly 4-5 g/kg) and, therefore, is classified as a dietary supplement, not a drug. It is most commonly available as a monohydrate in powder, candy, gum, and liquid. Numerous products combine it with vitamins, nutrients, and other supplements. Athletes usually "load" with 20 g creatine per day for 4-6 days (usually 5 g four times daily), followed by 2 g daily. Less is known about the optimal dose of CLA, but 3 g daily is commonly recommended.[5]

Conclusion

Support for using creatine and CLA, along with exercise, for improved body composition arises primarily from one study. While rigorously designed, such results require replication before use of such a program can be generally recommended. Oral supplementation with creatine alone has been studied extensively in athletes, with much less research in healthy non-athletes. Where resistance training has shown itself to be beneficial, some evidence supports the addition of creatine supplements. However, the early stage of this research must be noted, especially given the potential for complications in the elderly, especially those with co-morbidity. The evidence base to support CLA supplementation along with exercise is even smaller. Support comes primarily from animal studies, but these also reveal concerns about adverse effects. Much further research is needed into CLA before its use as a supplement should be promoted. ❖

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D Mommy + D Baby — Vitamin D and Preeclampsia

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

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Source: Bodnar LM, et al: Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab*. 2007;92:3517-3522.

THIS NESTED, CASE-CONTROL TRIAL WAS DESIGNED TO assess the independent effect of maternal 25-hydroxyvitamin D [25(OH)D] levels in early pregnancy on the risk of subsequent development of preeclampsia. Researchers were also interested in the newborns' vitamin D status.

Nulliparous pregnant women aged 14-44 years without preexisting medical conditions and with singleton pregnancies (n = 1198) were admitted into the trial and followed from < 16 weeks gestation to delivery at prenatal clinics and private practices. At enrollment, all subjects completed an interviewer-administered questionnaire regarding demographics, medical history, and health behaviors. Non-fasting blood samples were collected at typical clinically-indicated times, and medical record information was extracted to secure data on blood pressure and urinary protein measurements. Additional data and banked sera collected from women and newborns from 1997-2001 were used to complete the study, with 25(OH)D assays performed in 2006. Ideally, subjects' blood samples were available for evaluation from prior to 22 weeks gestation and pre-delivery, as well as a venous cord serum sample. The primary outcome measure was preeclampsia.

By trial's end, a total of 59 women had developed preeclampsia (4.9%). Adjusted serum 25(OH)D levels in early pregnancy were 15% lower in women who subsequently developed preeclampsia when compared with controls. After adjustment for potential confounders, a decrease in 25(OH)D level of 50 nmol/L doubled the risk of preeclampsia (OR = 2.4). As maternal 25(OH)D concentrations at < 22 weeks increased, the risk of preeclampsia decreased. Newborns of preeclamptic mothers were twice as likely as control newborns to have low 25(OH)D levels, with a significant correlation between pre-delivery maternal blood samples and cord samples. Findings were independent of confounders that included race/ethnicity and seasonality, and occurred in the context of widespread prenatal/multivitamin use among members of the cohort (93%). Bodnar and colleagues conclude that maternal vitamin D deficiency at < 22 weeks gestation is an independent risk factor for preeclampsia.

COMMENTARY

Preeclampsia occurs in 3%-8% of pregnancies, and is especially common in primigravidas and African-American (AA) women. It is typically defined as new-onset gestational hypertension and proteinuria that develops after 20 weeks gestation, with return of all abnormalities to normal by 12 weeks postpartum. The illness places both mother and fetus at risk.

Optimal 25(OH)D levels have been suggested but not definitively agreed upon, yet maternal vitamin D deficiency has been called a neglected public health issue, with studies suggesting almost 30% of AA women affected. This latter point is important due to the intersection of increased risk for preeclampsia and high rates of vitamin D deficiency states among AA women, suggesting a significant role for vitamin D.

Beyond health benefits to the mother associated with presumed optimal 25(OH)D levels that include potential cancer chemoprevention, healthy bones and possible protection against multiple sclerosis, and now prevention of preeclampsia, there are important implications for the newborn. Fetal 25(OH)D levels are entirely dependent upon the mother's stores of vitamin D, and neonatal vitamin D deficiency has been associated with

significant health issues that include skeletal problems, asthma, insulin-dependent diabetes, impaired growth, and schizophrenia.

Results from small trials have previously suggested a protective role for vitamin D against preeclampsia, but this is one of the first large, prospective investigations to explore the association between serum 25(OH)D levels and preeclampsia prior to symptom onset. The results are important, but weakened by the fact that calcium intake was not measured. It is known that low calcium states are a risk factor for vitamin D deficiency, and may also be a risk factor for preeclampsia.

Calls for further investigation into prenatal supplementation with vitamin D are appropriate, but many practitioners believe the time has come to institute this measure, especially for pregnant women with dark skin color for whom the risk of both preeclampsia and vitamin D deficiency is very high. It seems appropriate to supplement with additional vitamin D in early pregnancy beyond the amounts typically found in prenatal vitamins, especially over the winter months when less sun exposure can be expected. Broadly recommended intakes of vitamin D appear to be increasing monthly, but optimal levels for the pregnant woman have yet to be established. A daily dose of 1000 IU of vitamin D3 (cholecalciferol) seems a balanced general recommendation for expectant mothers in the absence of preexisting medical conditions or complicating factors. ❖

Does Black Cohosh Prevent Breast Cancer?

ABSTRACT & COMMENTARY

By Donald Brown, ND

Dr. Brown is Founder and Director, Natural Product Research Consultants, Inc; he serves on the Advisory Board of the American Botanical council and the President's Advisory Board, Bastyr University, Seattle, WA, and is an Advisor to the Office of Dietary Supplements at the National Institutes of Health; he is a consultant for Nature's Way, Inc.

Source: Rebbeck TR, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. *Int J Cancer*. 2007;120:1523-1528.

In a population-based, case-control study, women were asked about their use of "hormone-related" dietary supplements in an attempt to determine their association with risk of breast cancer. Participants included 949 breast cancer cases (mean age 63.0 years; 677 European American and 272 African American) and 1524 age-matched controls (mean age 61.8 years; 905 European American and 619 African American) from three counties of the Philadelphia metropolitan area. Women with ductal carcinoma in situ, lobular carcinoma in situ, and other nonmalignant tumor types were excluded. Controls could have no history of breast cancer.

Telephone interviews were used to collect information about the use of "hormone-related supplements" (HRS). Women were asked about the use of the following: Biest, black cohosh, Remifemin, DHEA, daidzein, dong quai, Estroven, genistein, ginseng, isoflavones, Promensil, red clover, Rejuvex, soy "medications," steroid creams, Triestrogen, and yam creams. Respondents could list up to five of these HRS used at least three times a week for one month or more any time before the reference date, which was defined as the date of diagnosis for the cases and the date of completion of the screening for the controls.

Use of HRS varied significantly by race, with African-American women being more likely than European-American women to use any herbal preparation (19.2% vs 14.7%, $P = 0.003$). Among the more commonly used preparations, African-American women were significantly more likely than European-American women to use black cohosh (5.4% vs 2.0%, $P = 0.003$), ginseng (12.5% vs 7.9%, $P < 0.001$), and red clover (4.7% vs 0.6%, $P < 0.001$). Use of other HRS (including Remifemin) was listed as being no more than 1% of women in the sample, with none reporting use of daidzein. Comparing women who took any HRS compared to those that did not, risk of breast cancer was significantly lower in the former (adjusted odds ratio 0.65, 95% CI: 0.49-0.87). Use of black cohosh had a significant breast cancer protective effect (adjusted OR 0.39, 95% CI: 0.22-0.70). This association was similar among women who reported either use of black cohosh or Remifemin (adjusted OR 0.47, 95% CI: 0.27-0.82). Although very preliminary, results suggested that the protective effect of black cohosh and/or Remifemin may be greater in the ER positive and PR positive groups compared to ER negative or PR negative tumors (these differences were small).

COMMENTARY

The answer to my somewhat provocative question in the title of this review is most likely "no." While surveys such as this suffer greatly by poor identification of sup-

plements (eg, not listing black cohosh and Remifemin in one category), this study does suggest that black cohosh does not seem to increase the risk of cancer as was feared following a mouse study.[1] It should also be noted that confounding factors, such as diet and physical activity, were not considered.

While data on the efficacy of black cohosh for vasomotor symptoms in menopausal women continue to be mixed, this large survey, coupled with previously reviewed safety data,[2] suggest black cohosh is a safe herbal supplement that is unlikely to qualify as an "HRS" due to data failing to demonstrate hormonal effects for the root extract. It should also be noted that the study did not find any correlation between risk factor and any of the other "HRS" reported.

Conclusions

Although the supplements studied in this survey were poorly identified, the results suggest that black cohosh does not increase risk of breast cancer and may possibly decrease risk. Controlled studies with at-risk populations are needed to confirm these preliminary findings. ❖

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Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. 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, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. Upon receipt of your evaluation, a certificate will be mailed.

CME Questions

1. **Conjugated linoleic acid (CLA) is generally available in the diet from:**
   a, fish oils.
   b. dairy products.
   c. chicken.
   d. None of the above

2. **The adverse effects in humans from conjugated linoleic acid (CLA) supplementation are:**
   a, poorly understood.
   b. well demonstrated to be very serious, with liver toxicity commonly reported.
   c. Well demonstrated to be non-existent.
   d. All of the above

3. **Beneficial effects of creatine and conjugated linoleic acid (CLA) supplementation with resistance training is supported by:**
   a, numerous large, randomized, controlled trials.
   b. anecdotal reports.
   c. a very small number of controlled trials.
   d. large numbers of epidemiological studies.

Answers: 1. (b); 2. (a); 3. (c)

Researchers find flaws in CAM-use studies

The methodologies of studies that find positive results from treating older, nondemented adults with complementary and alternative medicine (CAM) may deserve a second look, say researchers in the October 2007 issue of the *Journal of Clinical Psychiatry*. The researchers reviewed 33 studies and found the ones that had positive results often had substantial methodological limitations.

The researchers searched PubMed studies from 1966-September 1996 and PsycINFO studies from 1984-September 2006 using the combinations of terms including "depression," "anxiety," and "sleep; older adult/elderly," "randomized controlled trial," and a list of 56 terms related to CAM. They found 29 studies that met the inclusion criteria of sample size of 30 of more, treatment duration of two weeks or longer, and publication in English. Four more studies were added to the mix from manual bibliography searches.

The researchers reviewed the 33 articles for methodological quality using a modified Scale for Assessing Scientific Quality of Investigations (SASQI). A study was said to be positive if the CAM therapy proved significantly more effective than an inactive control (or as effective as active control) on at least one primary psychological outcome, the researchers say. They compared positive and negative studies on these characteristics: CAM treatment category, symptom(s) assessed, country where the study was conducted, sample size, treatment duration, and mean sample age.

Of the 33 articles reviewed, 67% were considered positive. These studies were found to have lower SASQI methodology scores than the negative studies. Mind-body and body-based therapies had somewhat higher rates of positive results than energy- or biologically-based therapies, the researchers say.

Overall, they conclude a few well-conducted studies suggested therapeutic potential for certain CAM interventions in older adults (such as mind-body interventions for sleep disturbances and acupressure for sleep and anxiety).

CAM use common in older adults

A recent study found that use of complementary and alternative medicine (CAM) in older adults is common, especially when they have health problems.

The researchers had three objectives in this study. They wanted to assess the prevalence and patterns of CAM use in a probability-based sample of older adults, describe the characteristics of older CAM users, and identify factors associated with complementary and alternative medicine use or nonuse. The researchers took a random sample of community-dwelling adults aged 65 or older from the Minnesota Driver's License/Identification Tape, using names from the Twin Cities seven-county metropolitan area. The adults in the survey received a questionnaire in the mail that included items on demographics, health status, health care utilization, CAM modality use, reasons for use, costs, and complementary and alternative therapy use satisfaction. The researchers then performed descriptive statistics, chi-square tests, and regression analysis on the data.

Overall, 62.9%, or 445, respondents reported use of one or more CAM modalities, with an average of three modalities. The top five CAM modalities used were nutritional supplements (44.3%), spiritual healing/prayer (29.7%), megavitamins (28.3%), herbal supplements (20.7%), and chiropractors (17.8%). The respondents noted that maintaining health and treating a health condition were the primary reasons for CAM use, with many using CAM to treat arthritis (44.4%) and chronic pain (23.5%).

Demographic variables were not significantly different between CAM users and nonusers, the researchers say. CAM users reported more unhealthy days than nonusers did, and overall satisfaction with CAM use was high (80%). The users say they were motivated to use CAM by symptoms of a health problem and desire for personal control over health. The main barriers to CAM use were lack of reason to use and knowledge of CAM. Only 53% of users disclosed CAM use to their primary care providers, a finding that concerned the researchers.

For more information about the survey, see the November 2007 issue of the *Journal of Alternative and Complementary Medicine*.

University of South Carolina establishes center to study CAM

The University of South Carolina in Columbia has received a $6 million grant from the National Institutes of Health to create a Center of Excellence for Complementary and Alternative Medicine Research on Autoimmune and Inflammatory Disease, one of 11 such centers in the nation.

Several research projects for the center are planned. Prakash Nagarkatti, PhD, Associate Dean for Basic Science at the School of Medicine, is the principal investigator for the grant and will lead the study on the mechanism by which resveratrol, a compound in the skin of red grapes, may help treat multiple sclerosis. Mitzi Nagarkatti, PhD, Chair of the Department of Pathology and Microbiology, will study how a compound in hemp may be useful in treating autoimmune hepatitis, and Lorne Hofseth, PhD, Assistant Professor in the SC College of Pharmacy, will study the anti-inflammatory properties of American ginseng in treating colitis. ❖

In Future Issues:

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