

Integrative Medicine

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the latest developments in integrative therapies [ALERT]

MEN'S HEALTH

ABSTRACT & COMMENTARY

Testosterone Therapy – Recommendations Resulting from Two Recent Clinical Trials

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

SYNOPSIS: Two recent cohort studies showed an increased risk for myocardial infarction and stroke when taking testosterone replacement therapy.

SOURCES: Vigen R, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310:1829-1836.

Finkle WD, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014;9:e85805.

The prescription rate of testosterone therapy has increased dramatically in the last decade,¹ and primary care practitioners are asked on a daily basis about testosterone supplementation. Ingenious marketing has led many patients — many of whom are older and have risk factors for heart disease — to question if testosterone therapy is right for them.²

Until recently, there were very few studies looking into the potential risks of testosterone therapy.³ In January 2014, the FDA issued a warning and stated that it was re-evaluating the effect of testosterone therapy on myocardial infarction (MI), stroke, and death.⁴ This reassessment is based on two recently published studies, as described below.^{5,6}

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VIGEN ET AL STUDY

This retrospective national cohort study was conducted on men who had their testosterone level checked and were undergoing coronary angiography within the VA hospital system.⁵ Data were extracted for the period of 2005-2011 from the VA electronic medical record system, VA administrative database, and VA laboratory files. The final cohort included men who had low testosterone (< 300), had never undergone testosterone replacement, and had undergone coronary angiography.

Patients with testosterone therapy use prior to coronary angiography were excluded, as were patients who started testosterone therapy prior to having a testosterone level checked or who were prescribed testosterone therapy after an MI. Patients with a hematocrit > 50%, a prostate-specific antigen > 4.0, or incomplete anatomical angiographic data were excluded.

Patients were considered to have started testosterone therapy if they filled a prescription for any formulation of testosterone after coronary angiogram. It was assumed that patients continued with the treatment until an outcome event occurred or the follow-up period ended. The primary endpoint of the study was time to all-cause mortality or hospitalization for MI or ischemic stroke.

As patients could not be randomized to testosterone therapy, stabilized inverse probability of treatment weighting was used to adjust for any unmeasured confounders that may have affected testosterone prescription. The final cohort was comprised of 8709 men with low testosterone. Of these, 1223 patients initiated testosterone therapy.

There was an overall high rate of comorbidities in the study population, but the patients starting testosterone therapy tended to be younger and have a lower rate of comorbidities.⁵ Testosterone therapy was started after a median of 531 days and the patients were followed for an average of 27.5 months. The Kaplan-Meier estimated cumulative percentages with primary endpoint events among

the no testosterone therapy group vs the testosterone therapy group at 1 year after coronary angiography were 10.1% vs 11.3%; at 2 years, 15.4% vs 18.5%; and at 3 years, 19.9% vs 25.7%. The absolute risk differences were 1.3% (95% confidence interval [CI], -7.1% to 9.7%) at 1 year, 3.1% (95% CI, -4.9% to 11.0%) at 2 years, and 5.8% (95% CI, -1.4% to 13.1%) at 3 years. There were no statistically significant differences between groups at any follow-up period except for a history of cerebrovascular disease.

FINKLE ET STUDY

This was a cohort study examining the risk of acute non-fatal MI following an initial testosterone therapy prescription in the Truven Health MarketScan Commercial Claims and Encounters Database.⁶ This database includes all health data licensed to Truven from fortune 500 companies, unions, and many other employers. Data from the period of 2006-2010 within the northeastern, north central, southern, and western United States was initially analyzed. Information related to why testosterone was prescribed was not available.

The investigators formed two cohorts from men who were enrolled in the database for a minimum of 22 continuous months. These groups were divided into men who had filled a prescription for testosterone and men who filled a prescription for phosphodiesterase type 5 inhibitors. The latter medication class was chosen as a comparison because it tends to have similar indications as testosterone, these medications are commonly prescribed in older men, they do not have androgenic effects, they are not metabolized to a sex steroid hormone, and they have not been associated with adverse cardiovascular events.

The investigators compared the incidence rate of MI in the 90-day period following the initial prescription with the rate in the 1 year prior to the initial prescription of testosterone therapy. They also compared post-/pre-rates in a cohort of men prescribed phosphodiesterase type 5 inhibitors. Testosterone supplementation post-/pre-rates were compared with

Summary Points

- FDA is re-evaluating safety of testosterone replacement therapy.
- Two recent cohort studies showed an increased risk for myocardial infarction and stroke when taking testosterone replacement therapy.
- Higher relative risk is seen mainly in older men with underlying coronary artery disease.
- Current studies have been retrospective or have had a small sample size; therefore, large randomized trials are required.

phosphodiesterase type 5 inhibitors post-/pre-rates. The main outcome of the study was acute MI. Patients with a history of MI prior to the initial prescription were excluded.

In this study, the adjusted rate ratio (RR) of myocardial infarction in patients prescribed testosterone therapy was 2.19 (95% CI, 1.27-3.77) in patients older than age 65 years and 1.17 in patients younger than age 65 years (95% CI, 0.84-1.63). By age, the RR was 0.95 (95% CI, 0.54-1.67) in patients under 55 years, 1.35 (95% CI, 0.77-2.38) in patients 55-59 years, 1.29 (95% CI, 0.71-2.35) in patients 60-64 years, 1.35 (95% CI, 0.44-4.18) in patients 65-69 years, 1.62 (95% CI, 0.51-5.16) in patients 70-74 years, and 3.43 (95% CI, 1.54-7.66) in patients older than 75 years. (*P* trend = 0.03).

The phosphodiesterase 5 inhibitor group baseline distribution of prior cardiovascular diagnosis, risk factors, and medication use was less than in the testosterone therapy group. This was adjusted with weighting with propensity scores. When comparing the testosterone therapy group to the phosphodiesterase 5 inhibitor group, the rate ratio was 1.90 (1.04-3.49) in those older than age 65 years and 1.10 (95% CI, 0.78-1.56) in those younger than age 65 years.

In men younger than age 65 years with a previous history of heart disease who were prescribed testosterone, the RR was 2.90 (95% CI, 1.49-5.62) vs 0.90 (95% CI, 0.61-1.34) for those without a previous history of heart disease. In men prescribed testosterone therapy who were older than age 65 years, the RR was 2.16 (95% CI, 0.92-5.10) for those who had a history of heart disease and 2.21 (95% CI, 1.09-4.45) for those without a history of heart disease. In men with a history of heart disease who were prescribed phosphodiesterase 5 inhibitors, the

RR was 1.40 (95% CI, 0.91-2.14) for those younger than age 65 years and 0.99 (95% CI, 0.84-1.17) for those older than age 65 years.

■ COMMENTARY

Testosterone replacement therapy is a common topic of discussion with middle-aged and older men. When abstracts of relevant articles spread through the medical media, many of us believed the results were going to change our practice. This thought seemed to be solidified by the fact that the FDA was further investigating the risk of cardiovascular events and death based on the two studies reviewed here. Now that we have been able to thoroughly look through these articles, what conclusions can be drawn?

In both studies the risk of myocardial infarction, stroke, and death was higher in the groups that were given testosterone replacement therapy. In the study by Finkle et al, there seemed to be an age-dependent effect, as the risk was higher in older men, with a trend of increased risk across age categories. This risk was even higher in older men with underlying cardiovascular disease.

The studies are based on data retrieved retrospectively, predisposing them to confounding and selection bias. Crucial clinical information is missing because of the study design. For example, we do not know if any of the study subjects met clinical criteria for hypogonadism, the time at which the samples were drawn, whether the results were confirmed by a second sample, and if any of the samples were obtained while a patient was ill. Follow-up information related to post-treatment testosterone levels, adherence levels, and clinical response was also poor. The pooled information was analyzed using complex computer models that could potentially increase hidden bias.

Proponents of testosterone replacement therapy might point out that there are studies which have found differing results:

- In 2012, one retrospective study investigated data from the VA medical records for 1031 patients.⁷ It was found that mortality was lower in men who were treated with testosterone compared with those who did not receive replacement therapy. The results may differ from the two studies analyzed due to the small sample size, no standardized time of testosterone testing, multiple testosterone formulations were utilized, and the main outcome was total mortality. There was a high rate of medical morbidity, with an average of 6.7 pharmacologically treated conditions. This included a 38% rate

of diabetes mellitus and 21% rate of coronary heart disease. This means that a majority of the study participants did not have a history of prior coronary heart disease and, based on the results found by Vigen and Finkle et al, are at decreased risk from testosterone replacement.

- Other studies have found that men who have endogenous testosterone concentrations in the middle to higher normal range have the lowest mortality and least likelihood of having a cardiovascular event.^{8,9} These same studies have also found that men who have low testosterone have an increased risk for cardiovascular events. Dogan et al also showed an inverse correlation between testosterone levels and atherosclerosis markers.⁸ We can conclude that low testosterone is bad and normal testosterone levels are beneficial. Should we offer replacement therapy for all patients with low levels? Not necessarily. The studies reviewed show that currently available testosterone formulations may not be safe for everyone.

On the other hand, multiple studies have established that there is a normal age-related decline in testosterone levels,^{10,11} and there is no consensus as to the exact cutoff for low testosterone. This is why currently available guidelines only recommend testosterone replacement for those who meet criteria for symptomatic hypogonadism. In my opinion, this means we should have a discussion about treatment outcome expectations and lifestyle modification prior to considering replacement therapy.

In summary, the data are conflicting and confusing.¹² Large, prospective, randomized trials are required before a valid consensus can be drawn, a consensus upon which we can frame our clinical practice. Until that time, many of our questions will not be adequately answered and, therefore, we are at the mercy of expert opinion.

One approach to navigate this uncertainty is by having an open conversation with our patients. Testosterone should only be measured in those who meet clinical criteria for hypogonadism. We should inform them that low testosterone levels may increase the risk of coronary heart disease and normal endogenous levels may decrease the risk of coronary heart disease. We do not yet know, with certainty, what impact exogenous testosterone may have, as some studies have shown benefit and others have shown increased risk, especially in those older than age 65 years and those with a prior history of coronary heart disease, regardless of age. Patients should be aware of normal decline in testosterone

levels related to age, as well as other normal age-related changes that could erroneously be attributed to low testosterone. Some patients may opt for a holistic approach that embraces lifestyle modification in lieu of testosterone replacement. We should advise patients on the benefits of a healthy weight, routine exercise, adequate sleep, avoiding tobacco products, limiting alcohol, stress management, and healthy eating.

Until more information is available, we can cautiously continue to offer testosterone replacement therapy in those who meet diagnostic criteria of hypogonadism after a thorough discussion about its potential risks and benefits. ■

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ABSTRACT & COMMENTARY

Massage for Neck Pain: How Much Is Optimal?

By *Melissa Quick, DO*

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

SYNOPSIS: Based on the results of Sherman's study alongside the conclusions of Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders, it seems that massage is a safe and generally useful modality for grade 1 and 2 neck pain.

SOURCE: Sherman KJ, et al. Five-week outcomes from a dosing trial of therapeutic massage for chronic neck pain. *Ann Fam Med* 2014;12:112-120.

This study was performed to assess the optimal amount of time massage should be used to improve neck pain in individuals suffering from chronic (> 3 months), non-specific neck pain. A total of 228 participants were randomized to one of six study groups (approximately 38 participants in each). The participants were between the ages of 20 and 64, both male and female, had to have at least one primary care visit for neck pain in the past 3-12 months, and had non-specific uncomplicated neck pain. Subjects were excluded if they had previous massage for neck pain in the last year or any massage in the last 3 months or complex neck pain (including disk herniation, motor vehicle accident, previous neck surgery, stroke, metastatic cancer, and many others).

This study examined five doses of massage that covered a broad range of feasible frequencies per week (1, 2, or 3 times) and treatment lengths (30 and 60 min). Five study groups received various doses of massage as the primary treatment (weeks 1-4), which consisted of a 4-week course of 30-minute visits 2 or 3 times weekly or 60-minute visits 1, 2, or 3 times weekly. The control group was randomized to a wait list during the primary treatment period and then received 6 weekly 60-minute massages *after* the primary treatment period in the secondary treatment period (weeks 5-10).

Study participants in the treatment groups received a total of 4-12 hours of massage and a total of 4-12 treatments, depending on their group assignment. Distinct massage protocols were defined for both the 30- and 60-minute massages to ensure that the massage therapist spent roughly the same proportion of time in each phase of treatment. Eight licensed massage therapists with at least 5 years of experience

Summary Points

- Neck pain is common and frequently chronic.
- Neck pain is the second most common reason individuals seek out complementary and alternative medicine (CAM).
- Massage therapy is the second most common CAM modality utilized for neck pain.

were trained in the study protocol and provided all massage treatments.

Treatment adherence was high — between 84-95% in all groups. The massage therapists were also specifically asked *not* to recommend self-care regimens, and at the end of the study, only 3.3% of participants reported doing self-care activities.

Primary outcomes were assessed at baseline and again at 5 weeks (a week after treatment completion) by telephone interviewers who were unaware of treatment assignment. The Neck Disability Index (NDI), a 10-item questionnaire, was used to assess neck pain and dysfunction and participants used a 0 (“no pain”) to 10 (“pain as bad as it can be”) scale to rate their pain at baseline and at all follow-up interviews.

Secondary outcomes measured days of restricted activity, global rating of improvement of pain, quantification of perceived stress (measured by a 10-item Perceived Stress Scale), and a single question about overall patient satisfaction.

The authors of the study acknowledge the inherent complexity of analyzing a six-arm dosing study, but chose a large sample size that allowed adequate power to detect significant differences between at least two of the five massage treatment groups.

For the primary outcome of the study — clinically relevant improvements in neck pain scores — the results indicate that the beneficial effects of 60-minute massages increased with dose and were especially evident for those receiving massage 2 or 3 times per week (2 x 60 min/wk: odds ratio (OR), 3.68; 95% confidence interval [CI], 1.13-11.98; $P = 0.03$; and 3 x 60 min/wk: OR, 5.53; 95% CI, 1.78-17.15; $P = 0.003$). Conversely, 30-minute massages, either 2 or 3 times a week, failed to provide significant benefits compared with the wait list control condition (2 x 30 min/wk: OR, 1.84; 95% CI, 0.5-6.81; $P = 0.36$; and 3 x 30 min/wk: OR, 1.37; 95% CI, 0.33-5.68; $P = 0.66$). Despite the differing significance of treatment duration and frequency, mean NDI scores improved in *all* massage groups compared to the control group after 5 weeks.

The only statistically significant finding for the secondary outcomes was the proportion of participants who reported their neck pain was much better or completely gone (omnibus $P < 0.001$). Three massage groups were significantly more likely to report this level of improvement than the control group: the 30 min x 3 times weekly group (OR, 20.4; 95% CI, 10.2-40.6); the 60 min x 2 times weekly group (OR, 18.9; 95% CI, 10.0-35.8), and the 60 min x 3 times weekly group (OR, 40.6; 95% CI, 27.8-59.5). Overall, the group with the most massage (60 min x 3 times weekly) had the most improved symptoms compared to every other treatment group.

■ COMMENTARY

Approximately 70% of the U.S. population experiences neck pain in their lives, and it often becomes episodic or chronic,¹ thereby negatively impacting individuals, their families, communities, businesses, and health care systems.² Indeed, neck pain is responsible for more than 10 million ambulatory medical care visits annually in the United States³ and is also the eighth leading cause of disability in the United States.⁴ Though conventional treatment options exist, neck pain is the second leading reason individuals seek out complementary and alternative medicine (CAM) treatments.⁵ Furthermore, massage therapy is the second most commonly used CAM treatment for neck pain.⁶

Although many etiologies of neck pain can arise from any of the structures in the neck, the vast majority of neck pain can be classified as “non-specific”

Table 1. Grades of Neck Pain Defined by the Neck Pain Task Force

Grade 1: neck pain with little or no interference with daily activities.
Grade 2: neck pain that limits daily activities.
Grade 3: neck pain accompanied by radiculopathy (“pinched nerve” pain weakness and/or numbness in the arm).
Grade 4: neck pain with serious pathology, such as tumor, fracture, infection, systemic disease; it was beyond the mandate of the task force to study Grade 4 neck pain.

— including degenerative changes, muscle spasm, ligamentous strain, etc. — and has no relation to specific disease or trauma.⁷ In general, non-specific neck pain does not require imaging, and importantly, research shows no correlation between degenerative changes seen on X-ray and pain levels.⁷

Until recently, defining neck pain and understanding appropriate treatment modalities had been vague, with a considerable amount of heterogeneity in the literature. However, the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders recently spent 7 years compiling a comprehensive review of the current state of neck pain research in an effort to elucidate a more clear and concise approach to neck pain. The task force concluded: 1) neck pain is common and frequently recurs; 2) there is typically no single cause and no single effective treatment for neck pain; 3) neck pain (including whiplash injuries) should be classified into four common grades (*see Table 1*); and 4) there are a variety of options *including massage* for Grade 1 or 2 neck pain.⁸

So, using the guidelines above, how should we treat neck pain? Many medical providers may begin with conventional medical recommendations such as rest, medications (especially NSAIDs), and physical therapy, but the evidence for long-term benefit of these modalities is lacking.⁹ Manual therapy presents as a useful adjunct to conventional treatment.

The task force reviewed more than 350 invasive and noninvasive studies on neck pain and concluded that “therapies involving manual therapy and exercise are more effective than alternative strategies for patients with neck pain,”⁹ hence validating the focus of Sherman’s study on the benefit of massage, one of the manual therapies. While many versions of manual therapy exist (chiropractic, osteopathic manipulation, etc.) and have their own inherent benefit, discussing modalities beyond massage therapy are beyond the scope of this article.

The word “massage” stems from both Arabic and Greek roots and means “to touch or squeeze softly.” Massage therapy has evolved since its origin more than 5000 years ago in India. Massage therapy is known as one of the earliest and most primitive techniques for pain relief and can be defined as a “therapeutic manipulation using the hands or a mechanical device in which numerous specific and general techniques are used in sequence, such as effleurage, petrissage, and percussion.”¹⁰

A 2012 Cochrane review assessing the effects of massage on mechanical neck disorders found that certain massage techniques (traditional Chinese massage, classical, and modified strain/counterstrain) were more effective than control for improving function and tenderness immediately post-treatment but do not have clinically applicable long-term conclusions.¹

One of the goals of Sherman’s study was to identify the optimal dose of massage therapy and, as such, the authors also focused on the feasibility of accessing and adhering to various massage therapy schedules. This study had an impressively high adherence rate: at least 95% in four massage dosing groups and 84% in the fifth group (30 minutes 3 times weekly), which speaks to the tolerability of this modality. The only groups with statistically significant outcomes for the primary variable were the longer, 60-minute massage groups, and even more benefit was seen in those who had hourly massages three times a week compare to just twice a week.

Interestingly, these results suggest a linear, dose-dependent relationship between the frequency and amount of time of a massage: longer, more frequent massages provide greater results. This is most evident in the secondary outcome of the NDI: for each additional weekly massage, there was an estimated -1.81-point improvement in NDI (95% CI, -2.52 to -1.10; $P < 0.001$) and an estimated -0.75-point improvement in neck pain intensity (95% CI, -1.01 to -0.47; $P < 0.001$). The authors of the study do not mention why they picked their specific frequencies and durations. A future study may provide more information as to where and when this linearity of frequency and duration ceases to be beneficial.

While impressive statistically, it is questionable if the general population would be able, both in terms of time and financial constraints, to achieve such dedicated adherence. In fact, though a handful of private insurance companies may cover some types of massage, the majority of insurance services (including Medicaid and Medicare) do *not* cover massage therapy, which can make this a difficult option for

many patients. Perhaps with more studies similar to Sherman’s, policy makers and insurers can move massage therapy into a more accessible modality. For reference, according to the American Massage Therapy Association, the average massage costs \$65 an hour.¹¹

Another aspect of Sherman’s study worth mentioning is that the massage therapists were specifically asked to *not* give advice or education to patients, presumably to ensure the results reflected *only* the effects of massage therapy. In a real clinical setting, however, Sherman acknowledges that self-care recommendations and education are commonly given to patients and likely serve as an adjunct to massage therapy. In a practical sense, self-care regimens and educational materials *are* low-cost, so for a patient with financial restraints, this option would be an attractive option to offer a patient.

One possible confounding factor in this study is that the majority of the study participants (55.3-73.7% per group) had prior personal experience with massage, which may have predisposed them to an anticipatory effect. On the other hand, each group had similarly low expectations that massage would be helpful (approximately 18% between all groups), which may indicate the participants did not garner any preconceived expectations from their participation in the study.

Finally, it is important to recognize potential risks in all treatments offered to patients. Thankfully, in general, massage is well-tolerated and quite safe.¹² Indeed, only 5.2% of the participants in Sherman’s study had an adverse event, most of which were related to increased spinal pain. Interestingly, the adverse event frequencies were similar between each group, suggesting that the duration or frequency of massage has no direct impact on adverse events.

Sherman’s study used well-trained massage therapists with a minimum of 5 years of experience. Before recommending a massage therapist to a patient, it may be beneficial to ensure your massage therapist has had the appropriate training and licensing. Currently, 43 states and Washington, D.C. regulate massage, and most require a minimum number of hours of training and successful completion of an exam.¹³

Based on the results of Sherman’s study and the task force conclusions, it seems that massage is a safe and generally useful modality for grade 1 and 2 neck pain. We can also extrapolate from this study that *any* dose of massage is better than none, based on the results that showed a global increase in mean NDI

scores in all massage groups except for the control group after 5 weeks.

Ultimately, when recommending treatment for neck pain, it is crucial to recall that there is no “best” treatment plan and a trial of a variety of therapies or a combination of therapies may be needed to achieve improvement of symptoms. Keeping that in mind, based on this study, it seems that when we recommend massage, longer treatments and greater frequency seem to have the most benefit if this is available to the patient. ■

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GASTROINTESTINAL DISORDERS

ABSTRACT & COMMENTARY

Managing Stress to Improve GERD Symptoms

By David Kiefer, MD

SYNOPSIS: A 4-week educational intervention about diet and stress for people with GERD showed improvement in perception and overall impact, but no change in scales that measured depression and anxiety.

SOURCE: Dibley LB, et al. Non-pharmacological intervention for gastro-oesophageal reflux disease in primary care. *Br J Gen Pract* 2010;60:e459-465.

The researchers' goal was to address the fact that therapies that are adjunctive to proton pump inhibitors (PPIs) for gastroesophageal reflux disease (GERD) have been under studied. In this clinical trial, an education intervention was examined in adult patients with GERD recruited from rural general practices in England. Inclusion criteria were a GERD diagnosis and taking PPIs for at least 6 months. Exclusion criteria included any other physical morbidity or a veto for participation by the primary care provider. A total of 179 patients agreed to participate in some aspect of this study.

The educational intervention was developed by reviewing proven programs from the medical literature, as well as from semi-structured interviews

Summary Points

- Thirty-nine patients completed 1.5 hour sessions weekly for 4 weeks focusing on dietary and stress factors related to GERD.
- Analyses 3 months after the completion of the education sessions showed improvements in the Brief Illness Perception Questionnaire and the Gastro-oesophageal Reflux Disease Impact Scale, though the Hospital Anxiety and Depression Scale did not change.
- Of note, there was no control group, randomization, nor blinding.

in 23 of the 179 participants. The interviews focused on aspects of the patients' GERD that concerned them and if the GERD was related to diet, alcohol, smoking, activity, posture, and dinner-to-bed time. The most commonly mentioned GERD-exacerbating factors were diet and stress, which then became the focus of the educational intervention.

Fifty-three people expressed interest in participating in the educational intervention. Of these, 42 were able to attend the four sessions, 1.5 hours weekly. At the first session and 3 months after the last session, the patients completed the Brief Illness Perception Questionnaire (BIPQ), the Gastro-oesophageal Reflux Disease Impact Scale (GIS), and the Hospital Anxiety and Depression Scale (HADS).

Data from 39 people were analyzed; the three patients with incomplete data were not included in an intention-to-treat analysis. After the intervention, the overall BIPQ decreased (37.5 to 18.0; $P < 0.001$), as did the GIS (18.0 to 14.0; $P = 0.008$). Of the eight domains contained within the BIPQ, all improved, except perception of the impact of the GERD on their lives or how long it would last. Both of these parameters were relatively high at baseline and deemed difficult to improve. As per the HADS, there was no significant change in depression (5.0 to 4.0; $P = 0.101$) nor anxiety (6.0 to 6.0; $P = 0.361$).

■ COMMENTARY

It is a bit tough to tease out the effects of dietary and stress education; both were involved in the intervention that was analyzed in this clinical trial. The authors highlight the improvements in illness perception and illness experience when the baseline results are compared to testing 3 months after the training was completed. It is true there were improvements, but the numbers were small ($n = 39$, though 42 should have been included statistically as intention-to-treat), and there was no control group. To validate and corroborate these findings, a control group, blinding, and randomization would be key in the next study.

Clinical Briefs in Primary Care and Pharmacology Watch Available Online

The December 2014 issues of *Pharmacology Watch* and *Clinical Briefs in Primary Care* are now available exclusively by e-mail or online. You can access these two valuable supplements to *Integrative Medicine Alert* at <http://www.ahcmedia.com/supplements/>. We will send PDF copies of these supplements to you by e-mail if you prefer. Please send an e-mail with your name and/or subscriber number to customerservice@ahcmedia.com with Digital AHC Supplements in the subject line.

What makes this study compelling is how it fits in with other research about the effect of stress on GERD symptoms. Studies have shown that GERD flares after traumatic events such as the World Trade Center attacks,¹ as well as with other stressors such as on-the-job stress.² This is probably mediated through nerves that connect the central nervous system (CNS) with plexi along the gastrointestinal tract.³ In some cases, stress via the CNS-gut connection can open the lower esophageal sphincter, a known physiological factor with GERD. But this doesn't always occur. For example, stress may worsen GERD even though the quantity and acidity of the refluxate doesn't change.³ In such cases, it is the perception of GERD that changes, hence, one rationale behind the intervention in the trial reviewed here. If an intervention, such as stress management, could affect the perception of GERD symptoms, then it could be a useful adjuvant to physiological shifts accomplished by pharmaceuticals. Interestingly, in this trial, the use of PPIs didn't change in the 3 months before the intervention compared to the 3 months after (statistics not provided), seeming to imply a stable acid physiology that was nudged toward improvement with the diet and stress management education. Of course, this is mostly conjecture, and there are likely many factors involved. Nonetheless, this pilot trial showed some positive effects to this intervention, and there is likely little downside except for the time commitment and cost of leading the educational sessions. It behooves the health care provider to inquire about the presence of stress in any of their patients with GERD, and then take the next step and brainstorm with them about what can be done about it. ■

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SHORT REPORT

Dietary Flavanols from Cocoa Improve Dentate Gyrus Function and Cognitive Performance in Aging Population

By *Carrie Decker, ND*

Founder and Medical Director, Blessed Thistle, Madison, WI

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

SYNOPSIS: Age-related decline in dentate gyrus activity and associated cognitive function is improved over a 3-month period by a diet including high amounts dietary flavanols from cocoa.

SOURCE: Brickman AM, et al. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. *Nat Neurosci* 2014 Oct 26; [Epub ahead of print].

Decline in functional integrity of the dentate gyrus, a hippocampal region, has been observationally seen with aging.¹ However, beyond these correlations, direct association between cognitive decline, dentate gyrus function, and the effects of non-pharmacological interventions has not been demonstrated. This study was designed to assess the effects of a high flavanol dietary intervention and exercise on dentate gyrus function and cognitive performance.

A population of 41 healthy but sedentary 50- to 69-year-old subjects were randomly assigned to interventions of high dietary flavanols (900 mg cocoa flavanols and 138 mg of epicatechin per day) and active exercise, high dietary flavanols and no exercise, low dietary flavanols (10 mg cocoa flavanols and < 2 mg epicatechin per day) and active exercise, or low dietary flavanols and no exercise for a duration of 12 weeks. Active exercise consisted of 1-hour exercise sessions, including 40 minutes of aerobic activity four times a week. Exercise was performed at a target heart rate of 65-80% of each participant's maximum heart rate for weeks 4 through 12 of the study, gradually ramping intensity in the weeks prior to this. There were no other dietary interventions, and individuals who used dietary supplements regularly were excluded from the study. Both participants and observers were blinded to intervention randomization.

Cerebral blood volume (CBV) measurement by functional magnetic resonance imaging is routinely used to measure changes in brain activity² and is an established correlate of neuronal metabolism. The Benton Visual Retention Test (BVRT) has been shown to stimulate dentate gyrus function.³ However, in healthy individuals, a ceiling effect exists, and modifications were integrated to the test

Summary Point

- Daily consumption of high amounts of dietary flavanols from cocoa has been shown to improve cognitive task performance and increase cerebral blood volume to the dentate gyrus.

to eliminate this limitation. The primary outcomes of the modified BVRT and CBV were utilized to assess subjects both prior to and upon completion of the 12-week intervention period. At the end of the 12-week intervention, it was found that the high flavanol intervention had a significant effect on the modified BVRT performance, independent of exercise. Modified BVRT reaction times of the high flavanol group were 1997 ms compared with 2627 ms for the low flavanol group ($P = 0.038$). Preliminary data acquired from a general healthy population (ages 21-69 years) showed that the modified BVRT reaction time worsens with age, at approximately 220 ms per decade. The improvement seen with the high flavanol intervention is comparable to 2-3 decades of aging. No significant effect of the exercise intervention was seen in the modified BVRT performance. A significant increase in CBV in the dentate gyrus was also seen with the high flavanol intervention ($P = 0.042$), but the exercise intervention had no effect. Changes in the modified BVRT performance were shown to be correlated with CBV to the dentate gyrus.

In addition to positive benefits that chocolate consumption offers for cardiovascular health,⁴ this study offers further reason to consider chocolate in moderation as a part of a healthy diet. Flavanols are

currently not a part of package labeling of chocolate; however, there are some flavanol-enriched products that do display this information on their label. Natural cocoa solids are high in flavanols. However, as flavanols are associated with bitterness, they may be processed out of chocolate products, particularly by the process of ditching.⁵ The amount of flavonoids in chocolate products range from the low end of approximately 26 mg per serving of chocolate syrup to 227 mg per serving of cocoa powder or baking chocolate.⁶ In general, flavanol content is correlated with percent cacao content of chocolate, so do consider this with your holiday snacking! ■

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MEMORY AND COGNITIVE FUNCTION

SHORT REPORT

Pay Attention! Tai Chi Can Help

By David Kiefer, MD

SYNOPSIS: A 15-week course in tai chi improved attention scores in healthy university students.

SOURCE: Converse AK, et al. Tai chi training reduces self-report of inattention in healthy young adults. *Front Hum Neurosci* 2014;8:13. doi:10.3389/fnhum.2014.00013.

These researchers were interested in studying mind-body techniques for their effectiveness in treating attention deficit hyperactivity disorder (ADHD), as alternative or adjunctive treatments to pharmaceuticals. The mind-body technique that was the focus of this study was tai chi, a time-honored series of slow-flowing movements incorporating a mindful attention to the body. Their background references point out the proven health benefits, including psychological components and physical outcomes, but most of these have been in middle-aged to older adults. Could these positive effects be extended to another demographic? Students aged 18-34 from the University of Wisconsin-Madison campus were recruited to participate in this trial; 34 were students of a tai chi class (the treatment group) and 57 were from a psychology class (the control group). There were no exclusion criteria. The treatment group attended 50-minute classes twice weekly for 15 weeks in order to learn the 24-form Yang sequence, a type of tai chi. Research participants in each group underwent 1-hour testing three times during the 15 weeks; the testing quantified balance (one-legged stand test) and cognition (the spatial working memory testing, stop signal testing, and reaction time [RT] variability in the affective go/no-go test [AGN]). Study participants also completed four questionnaires: demographics, the Adult ADHD Self-Report Scale (ASRS), experience with mind-body practices, and exercise amount. A total of 28 and 44 students completed the tai chi and control classes, respectively, which were not analyzed

Summary Point

- After twice weekly tai chi classes for 15 weeks, students fared better than a control group in the inattention subset of a standardized ADHD scale; other parameters did not improve.

by intention-to-treat. The tai chi group showed improvements in the ASRS and the AGN scores from the beginning to the end ($P = 0.006$). These results were further analyzed; inattention (as per the ASRS) in the tai chi group was 10% less than the controls ($P = 0.044$), but a separate component of ADHD, hyperactivity, and impulsivity didn't change. There was also a correlation with RT variability in the AGN test and inattention, both corroborating findings in prior research (showing that RT variability might be an indicator for ADHD) and the believability of the tai chi effect. These are interesting effects, in that this study is one of the few in healthy young adults, and the results may extrapolate to people with ADHD due to the findings in the particular subsets. Yes, there were issues with the methodology, including the lack of an intention-to-treat analysis and the lack of blinding. However, maybe this modality and other mind-body movement therapies will work their way into our treatment tool box for inattention and/or hyperactivity. ■

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CME QUESTIONS

1. **Serum testosterone measurement is appropriate for which patient groups?**
 - a. All men over age 40
 - b. Symptomatic men without a history of coronary heart disease
 - c. Older men with fatigue
 - d. All men with erectile dysfunction
 - e. Men who meet clinical criteria for hypogonadism
2. **Which of the following is true regarding non-specific neck pain?**
 - a. Cervical X-rays are recommended prior to initiating treatment.
 - b. Massage therapy is a safe option in treating neck pain.
 - c. Neck pain is usually an isolated event in an individual's life.
 - d. There is usually one single cause for neck pain.
3. **When testing was done 3 months after the gastroesophageal reflux disease (GERD) educational intervention was completed, which of the following is true?**
 - a. All aspects of the Brief Illness Perception Questionnaire improved, except perception of the impact of the GERD on their lives or how long it would last.
 - b. The Hospital Anxiety and Depression Scale (HADS) anxiety subset increased by 20 points.
 - c. The HADS depression scale dropped significantly by 3 points.
 - d. The researchers ended up not collecting data for the Gastro-oesophageal Reflux Disease Impact Scale.
4. **Daily consumption of high levels of dietary flavanols has been shown to improve:**
 - a. dentate gyrus cerebral blood volume and cognitive performance.
 - b. dentate gyrus cerebral blood volume but not cognitive performance.
 - c. cognitive performance but not dentate gyrus cerebral blood volume.
 - d. neither dentate gyrus cerebral blood volume nor cognitive performance.
5. **Which of the following parameters improved in the participants of a 15-week tai chi class?**
 - a. Spatial working memory testing
 - b. Adult ADHD Self-Report Scale
 - c. Stop signal testing
 - d. Math scores

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.

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