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Alternative Medicine

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis

Osteoarthritis (OA) is the most common of the arthritic conditions, affecting at least 20 million Americans. The dietary supplements glucosamine and chondroitin are advocated as safe and effective options for the management of OA.

This was a multi-center, double blinded, placebo and celecoxib controlled trial, named the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) which evaluated the efficacy and safety of glucosamine/chondroitin as a treatment for knee pain from osteoarthritis.

Eligible patients were at least 40 years of age and had clinical and radiographic evidence of OA. The authors screened 3,238 patients for inclusion in the study, and after exclusion criteria, they randomized 1,583 patients to one of five groups. The patients were randomly assigned as follows; placebo group 313 patients, glucosamine alone 317 patients, chondroitin alone 318 patients, glucosamine plus chondroitin 317 patients, and celecoxib 318 patients.

Patients took their respective treatments for 24 weeks. Patients were allowed to take up to 4000mg of acetaminophen daily, except during the 24 hours before a clinical evaluation for joint pain. All other analgesics, including narcotics and NSAIDS were not permitted.

The primary outcome measure was a 20% reduction in knee pain from baseline to week 24. The authors found that for mild knee pain, glucosamine +/- chondroitin was not significantly more effective than placebo, however for moderate to severe pain, the response to combined glucosamine/chondroitin therapy was significantly higher than placebo (79.2% vs 54.3%). Celecoxib had a 69.4% response at 24 weeks.

The authors conclude that glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. Exploratory analyses sug-

gest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate to severe knee pain.

Clegg et al, New England Journal of Medicine, February 23, 2006. NEJM 2006;354:795-808

Editors note: In this trial, the data also showed a superior response of glucosamine/chondroitin to celecoxib (79.4% vs 69.4%) in patients with moderate to severe pain. These results do warrant further study. – MSB

Cardiology

Cocoa Intake, Blood Pressure and Cardiovascular Mortality

This was an observational study of elderly men to evaluate the association with cocoa intake on high blood pressure and cardiovascular mortality.

Initially 1,266 men aged 65 to 84 were invited to participate in the study, of which 939 agreed to participate in the study. Men with cardiovascular disease, cancer, diabetes, or who were taking anti-hypertension medications were excluded. The resulting study population consisted of 470 men.

The patients were interviewed in 1985, 1990 and 1995 regarding their habitual consumption of foods in the preceding week. Interviews were conducted by experienced dietitians, with the person preparing the patient's food present, and verified with the quantities of food bought per week.

Mortality between 1985 and 1990 was related to cocoa intake reported in 1985; mortality between 1990 and 1995 was related to cocoa intake reported in 1985 and 1990; mortality between 1995 and 2000 was related to cocoa intake reported in 1985, 1990 and 1995.

One third of the men did not consume cocoa. Plain chocolate and chocolate bars contributed to 2/3 of the total cocoa intake. The mean cocoa intake of the lowest tertile (n=165) was 0g/day, middle tertile (n=149) mean was 0.92g/day (0.60–1.45), and the highest tertile

(n=156) mean was 4.18g/day (2.90-6.10).

After adjusting for age and other confounding factors, the authors found that mean systolic blood pressure was 3.7mm hg lower (-7.1 to -0.3mm hg) in the highest tertile of cocoa consumption compared with the lowest tertile of cocoa consumption. The mean diastolic blood pressure was 2.1mm hg lower (-6.2 to 0.2) in the highest tertile of cocoa consumption compared with the lowest tertile of cocoa consumption.

The relative risk of mortality from cardiovascular disease (CVD) was 1.00 for the lowest tertile, 0.79 for the middle tertile, and 0.50 for the highest tertile. The relative risk of mortality from all causes was 1.00 for the lowest tertile, 0.79 for the middle tertile, and 0.52 for the highest tertile. Both were adjusted for multiple factors including age, smoking, alcohol consumption, use of anticoagulants, body mass index and several dietary factors.

The authors conclude that in a cohort of elderly men, cocoa intake is inversely associated with blood pressure and 15 year cardiovascular and all-cause mortality.

Buijsse et al, Archives of Internal Medicine, February 27, 2006. Arch Int Med;2006;411-417

Editors note: Many of us are delighted with the results of this study. – MSB

Comparison of Accuracy of 64-Slice Cardiovascular Computed Tomography With Coronary Angiography in Patients With Suspected Coronary Artery Disease

This study evaluated 64-slice cardiovascular computed tomography (CVCT) to direct coronary angiography. The purpose was to evaluate if CVCT can replace coronary angiography in select clinical situations.

The study population consisted of 66 sequential patients. The study population had 32 men, and the patient average age was 62. The patients had recently completed 64-slice CVCT angiography and direct catheter angiography for suspicion of obstructive coronary artery disease. Subjects were referred to CVCT by their cardiologist or primary care provider after presentation of symptoms, or after results of nuclear perfusion testing supported myocardial ischemia.

Results from catheter angiography and CVCT were analyzed independently by two expert readers who were blinded to each other's opinion. The left main, left anterior descending, left circumflex and right coronary arteries and their branches were evaluated. Where applicable, vein graft patency was also evaluated.

Sixty-four slice CVCT identification of lesions with

>50% stenosis within measured coronary vessels showed a sensitivity of 95%, specificity of 96%, positive predictive value of 97%, and a negative predictive value of 92%. There was 100% agreement on evaluation of vein grafts. Calculations of left ventricular ejection fraction were nearly identical (58.7% and 58.6%) between CVCT and catheter angiography.

The authors conclude the results of this study suggest that the 64-slice cardiovascular computed tomography scanner has the ability to non-invasively detect significant atherosclerosis in a reliable and accurate manner.

Fine et al, American Journal of Cardiology, January 15, 2006. Am J Cardiol 2006;97:173-174

Editors note: Non-invasive technology continues to improve. – MSB

Emergency Medicine

The San Francisco Syncope Rules vs. Physician Judgement and Decision Making

Syncope is a transient loss of consciousness followed by a return to pre-existing neurological function. Between 1% and 2% of emergency department visits and hospital admissions are related to a transient loss of consciousness.

The San Francisco Syncope Rules (SFSR) are designed to stratify syncopal patients into high risk or low risk for a potential serious outcome, and hospital admission. The rules are:

- 1) Systolic blood pressure less than 90 at the time of triage
- 2) Shortness of breath
- 3) History of congestive heart failure
- 4) EKG showing a rhythm that is not sinus or new EKG changes
- 5) Hematocrit less than 30%.

No to all the above is considered low risk for a serious outcome, while yes to any of these is considered a high risk for serious outcome requiring admission.

This was a prospective, cohort study designed to compare the San Francisco syncope rules to physician judgement. Physicians evaluated patients with syncope, and predicted the chance (0-100%) of the patient developing a predefined, serious outcome. They were then observed to determine their decision to admit the patient.

During the study period there were 684 ED visits for syncope, and 79 visits resulting in serious outcomes. The authors found that physician judgement showed

94% sensitivity, and 52% specificity. The SFSR showed 96.2% sensitivity and 61.9% specificity. The SFSR would have resulted in an absolute decrease in admissions of 10% of the patients in the low risk group, without missing a serious outcome.

The authors conclude that physician judgement is good when predicting which patients with syncope will develop serious outcomes, but contrary to their judgement, physicians still admit a large number of low-risk patients. The SFSR performs better than current physician performance and has great potential to aid physician decision making. – MSB

Quinn et al, The American Journal of Emergency Medicine, October 2005. Am J Emerg Med, 2005;23:782-786

The Utility of Routine X-Rays in all Glass-Caused Wounds

Patients with glass injury account for 13% of traumatic wounds. Glass has been shown to be radio-opaque on plain film x-rays. It is common practice to routinely obtain x-rays before clinical evaluation and cleaning of glass-caused wounds to assess for possible retained foreign bodies.

This was a prospective study designed to look at the necessity of plain x-rays for all patients with glass-caused wounds. Patients were eligible for inclusion if they sustained five or less glass-caused wounds within 72 hours of presentation. Patients who were unwilling or unable to give informed consent were excluded. Following triage, patients received standard anterior-posterior and lateral plain films of the area. The results of the x-ray reading were not discussed with the wound care provider until after the clinical examination was complete.

Following informed consent, the wounds was palpated for foreign bodies, then anesthetized. Further exploration was completed using a hand-held metal probe, and visualization of the wound was carried out as completely as possible. A superficial wound was defined as no deeper than the subcutaneous fat, and a deep wound was defined as deeper than subcutaneous fat. An x-ray was deemed to be beneficial on any wound where more foreign bodies (FB) were detected than were found on clinical examination. Wounds with no more FB's found on x-ray than clinical examination were not beneficial.

There were 264 wounds total during the study period, of which 238 (90.2%) could be completely visualized or

probed, and 26 (9.8%) could not. Of the 264 wounds, 134 were superficial and 130 were deep wounds. Of the 134 superficial wounds, 8 had foreign bodies, and 2 x-rays were beneficial (1.5%). Of the 130 deep wounds, 15 had foreign bodies, and 10 x-rays were beneficial. There were 105 (80.8%) deep wounds that could be adequately explored, and 7 (6.7%) x-rays were beneficial, while 25 of the deep wounds could not be explored and 3 (12.0%) of the x-rays were beneficial.

The authors conclude that in light of the benign nature of the 2 superficial wounds in which a foreign body was missed clinically, and that there exists a subset of glass-caused wounds that are superficial and adequately explored, and, therefore, do not need routine x-rays. – MSB

Orlinsky & Bright, The American Journal of Emergency Medicine, March 2006. Am J Emerg Med, 2006;24:233-236

Nephrology

Use of Allopurinol in Slowing the Progression of Renal Disease Through it's Ability to Lower Serum Uric Acid Levels

Hyperuricemia is strongly associated with the development of hypertension, cardiovascular disease and the progression of renal disease. Allopurinol decreases serum uric acid levels by inhibiting xanthine oxidase. In animal studies, correction of hyperuricemia has improved blood pressure control, decreased proteinuria, and decreased the progression of renal failure.

This was a randomized, prospective, controlled study. Between April 2003 and April 2004, 852 patients followed in renal clinic were screened for participation in the study. All patients has renal disease defined as daily proteinuria greater than 0.5g, and/or serum creatinine greater than 1.35mg/dl. Patients were in stable clinical condition in terms of their general health, and baseline creatinine and proteinuria had not increased by greater than 40% within the three months before screening. Patients were excluded if they had a history of gouty arthritis, renal stones, or a creatinine > 4.5mg/dl. Patients already on allopurinol or azathioprine treatment for any reason at screening, those with a history of allopurinol hypersensitivity, women of childbearing age unwilling to use effective means of contraception, and pregnant or lactating women were also excluded. Two hundred seventy-six patients satisfied the initial screening criteria, and were screened for hyperuricemia, defined as a serum uric acid level greater than 7.6mg/dl.

An ultrasound was performed on eligible patients to rule out obstructive uropathy or renal stones.

Fifty-four patients met inclusion criteria, agreed to participate in the study and were randomized into treatment or control groups. The mean age of the allopurinol group was 47.7 + 12.9 years, the control group 48.8 + 16.8 years. Diabetes was present in 24% of the treatment group and 27% of the control group, pre-existing hypertension was present in 83% of the treatment group and 73% of the control group. Patients received starting doses of 200mg/day of allopurinol if their serum creatinine was less than or equal to 1.7mg/dl, and 100mg/day if their serum creatinine was greater than 1.7mg/dl. Allopurinol was then adjusted to maintain serum uric acid levels in a normal range. Dosages of antihypertensive drugs, lipid lowering agents, and steroid or cytotoxic agents were continued and adjusted to the individual patients clinical condition.

Three patients dropped out of the study. One patient in the treatment group developed an urticarial skin rash, and two control group patients did not return for scheduled follow-up visits.

There was a significant drop in the uric acid levels in the treatment group, from 9.85 + 1.18mg/dl to 5.88 + 1.01mg/dl. The patients in the control group maintained elevated uric acid levels from 9.92 + 1.68mg/dl at baseline and 10.08 + 1.68 at the end of the study. Baseline creatinine levels were 1.64 + 0.63 in the treatment group, and 1.86 + 0.69 in the control group. At the end of the 12 month study period, the creatinine level in the treatment group was 1.99 + 0.92, and the creatinine in the control group was 2.89 + 0.96. In the treatment group, 21/25 (84%) of patients maintained stable renal function, 3/25 (12%) had worsening renal function and 1/25 (4%) reached end stage renal failure and required dialysis. In the control group, 14/26 (53.8%) of patients maintained stable renal function, 11/26 (42.3%) of patients had worsening renal function, and 1/26 (3.8%) reached end stage renal disease and required dialysis.

The authors conclude that allopurinol therapy significantly decreases serum uric acid levels in hyperuricemic patients with mild to moderate chronic kidney disease. Its use is safe and helps preserve kidney function during 12 months of therapy compared with controls. Results of this study need to be confirmed with an additional prospective trial involving a larger cohort of patients to determine the long-term efficacy allopurinol therapy and in specific chronic kidney disease sub-populations.

Siu et al, American Journal of Kidney Diseases, January 2006. Am J Kidney Dis 47:51-59

Editors note: A well done study which shows promise. As the authors point out, the results need to be confirmed with other long term, prospective studies. – MSB

Neurology

Oral Contraceptives and Increased Headache Prevalence – The Head Hunt Study

It is well known that alterations in female sex hormones may influence headache. The prevalence of migraine increases among girls during adolescence and early adulthood. Many women experience attacks related to menstruation and in the majority of women with migraine, the condition improves with pregnancy. This was a population-based study designed to look at the association between migraine headaches and the use of estrogen containing oral contraceptives (OC). All female residents of Nord-Trondelag County, Norway who were 20 years of age or older were invited to participate in the study. There were 46,405 women invited to participate in the study, of which 74% agreed to participate. Two questionnaires containing more than 200 health related questions were administered to participants.

If the women answered yes to having had a history of headaches, 12 additional questions were asked which were designed to determine whether the headaches were migraine or non-migrainous. Women were also asked if they were menstruating, and if they answered yes and were <56 years old, they were subsequently asked about present and past OC use.

The authors found that the relative risk of migraine headache in users of oral contraceptives was 1.4 (1.2 - 1.7), and the risk of non-migrainous headache was 1.2 (1.0 - 1.4). The risk of migraine headache in previous OC use was 1.2 (1.0 - 1.3) for migraine headaches, and 1.1 (1.0 - 1.2) for non-migrainous headaches. The authors could not demonstrate a dose relationship between headaches and the amount of estrogen contained in the OC's.

The authors conclude that headache, especially migraine, was more likely among pre-menopausal women using oral contraceptives containing estrogen. – MSB

Aegidius et al, Neurology February 14, 2006. Neurology 2006;66:349-53

Occupational Medicine

A Randomized Clinical Trial of Continuous Low Level Heat Therapy for Acute Muscular Low Back Pain in the Workplace

Low back pain is one of the most costly and difficult medical problems in industrialized countries, with a prevalence of 25% to 30% in an adult life span and an incidence of about 5% a year. Approximately 50% of working-age individuals in the United States report back symptoms each year, with annual societal costs of back pain estimated to be between \$20 to \$50 billion.

The authors sought to compare the therapeutic benefits of heat wrap therapy combined with an educational program to an education-only program on reducing pain and disability from acute work-related low back pain.

Potential study participants included employees of a medical facility with approximately 19,000 employees, including approximately 6,000 involved in direct patient care. Full time employees who sustained an acute episode of low back pain from September 1, 2002 to August 31, 2004 and met all eligibility criteria were invited to participate in the study. Forty-three employees met inclusion and exclusion criteria and were randomized to one of the two study groups. There were 18 patients in the education only group, and 25 patients in the heat wrap plus education group.

The heat wrap group wore a heat wrap for three consecutive days. The heat wraps were 104°F (40°C) and worn for eight daytime hours. The heat wrap was removed at the end of each day. A new heat wrap was applied on each of the three days.

After adjusting for age, sex, pain medication use, and baseline pain intensity, the authors found that the heat wrap group has significantly reduced pain intensity, increased pain relief and improved disability scores during and after treatment with heat wraps.

The authors conclude that the results of this study demonstrate that heat wrap therapy significantly reduced pain intensity, increased pain relief and improved disability scores. Further studies may be needed to evaluate interactions such as the interaction between heat wrap therapy and age with larger sample sizes, which would help to answer an important question whether heat wrap therapy can have different effects in different age groups.

Tao et al, Journal of Occupational & Environmental Medicine, December 2005. J Occup Environ Med 2005;47:1298-1306

Editors note: This was not blinded, or placebo controlled. Studies in treating back pain are difficult to do, which explains the wide variation of results in the literature. – MSB

Pediatrics

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

Human rotavirus is a leading cause of diarrhea-related illness and death among infants and young children. Annually, rotavirus is associated with 25 million clinic visits, two million hospitalizations, and more than 600,000 deaths worldwide among children younger than five years of age.

This was a randomized, double blinded, placebo controlled study which evaluated the safety and efficacy of an attenuated G1P[8] human rotavirus vaccine (HRV). A total of 63,225 (31,673 vaccine and 31,552 placebo) infants ages 6 to 13 weeks, from 11 Latin American countries and Finland received either two oral doses of either HRV vaccine or placebo. All infants were part of the safety study, while the vaccine's efficacy was studied in a subgroup of 20,169 infants (10,159 vaccine and 10,010 placebo).

In evaluating the vaccine's efficacy, the authors found that in the vaccine group, 12 infants developed severe rotavirus gastroenteritis and 9 infants required hospitalization. In the placebo group, 77 infants developed severe rotavirus gastroenteritis, and 59 required hospitalization. For all types of gastroenteritis, 183 infants in the vaccine group developed severe gastroenteritis, with 145 requiring hospitalization, while the placebo group 300 infants developed severe gastroenteritis, and 246 required hospitalization. The risk of intussusception was the same in both groups.

The authors conclude that two oral doses of live, attenuated G1P[8] vaccine were highly efficacious in protecting infants against severe rotavirus gastroenteritis, significantly reduced the rate of severe gastroenteritis from any cause, and were not associated with an increased risk of intussusception. – MSB

Ruiz-Palacios et al, New England Journal of Medicine, January 5, 2006. NEJM 2006;354:11-22

Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine

This was a randomized, double blinded, placebo controlled study designed to evaluate the safety and

efficacy of a different human rotavirus vaccine (HRV) than evaluated in the above paper. Healthy infants between the ages of 6 and 12 weeks were eligible. Infants were excluded if they had received oral polio vaccine during the 42 days preceding the planned first dose, or if it was anticipated that oral polio vaccine would be administered during the study. All other licensed vaccines and breast feeding were not restricted. Infants were randomly assigned to receive three 2ml doses of vaccine or placebo 4 to 10 weeks apart.

In the vaccine group (34,035 infants), 20 of 34,035 infants required hospitalization and emergency department visits. In the placebo group, 383 of 34,003 infants required hospitalization and emergency department visits. For the subgroup of rotavirus of any severity, in the vaccine group 83 of 2,834 infants in the vaccine group, and 318 of 2,839 infants in the placebo group developed rotavirus gastroenteritis. The rate of intussusception was similar in the two groups.

The authors conclude that this vaccine was efficacious in preventing rotavirus gastroenteritis, decreasing severe disease and health care contacts. The risk of intussusception was similar in vaccine and placebo recipients. – MSB

Vesikari et al, New England Journal of Medicine, January 5, 2006. NEJM 2006;354:23-33

Surgery

Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men

Many men with inguinal hernias have minimal symptoms. Whether deferring surgery is a safe and acceptable option has not been assessed.

This was a randomized, multi-center trial which compared watchful waiting to surgical hernia repair in minimally or asymptomatic men at two years. Participants were 18 years or older, and presented with asymptomatic or minimally symptomatic inguinal hernias. The authors screened 3,074 men, of which 1,447 were ineligible, and 903 refused consent. Subsequently 724 men were randomized to receive either surgery (358 men) or watchful waiting (366 men). Interestingly, 62 men in the surgery crossed over into the watchful waiting group, and 85 men in the watchful waiting group crossed over into the surgery group. Demographics, including age, race, education, insurance status and employment status were similar in both groups. Baseline health status was similar in both

groups.

At two years, pain limiting activities was 5.1% in the watchful waiting group, and 2.2% in the surgical repair group. The difference was not statistically significant. The difference in the physical component score (0.29 points vs 0.13 points) was also not statistically significant. One watchful waiting patient experienced acute incarceration without strangulation at two years. A second watchful waiting patient had hernia incarceration with bowel obstruction at four years. Recurrence of inguinal hernia occurred in five of the surgical repair patients.

Post-operative complications occurred in 85 (22.3%) patients, and included wound hematoma (23 [6.1%]), scrotal hematoma (17 [4.5%]), urinary tract infection (8 [2.1%]), wound infections (7 [1.8%]), orchitis (6 [1.6%]), seromas (6 [1.6%]), urinary retention (1 [0.3%]), and “other minor complications” (22 [5.8%]). There were three patients who experienced life threatening, post-operative complications; bradycardia, deep vein thrombosis and post-operative hypertension requiring hospitalization.

The authors conclude that watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias. Delaying surgical repair until symptoms increase is safe because acute hernia incarcerations rarely occur.

Fitzgibbons et al, Journal of the American Medical Association, January 18, 2006. JAMA 2006;295:285-292

Editors note: In spite of the surgical complications, the surgery patients did fare better at two years, but this difference was not statistically significant. This does warrant a larger study. In the interim, treatment should be individualized to the patient's wishes and their risk for surgery. – MSB

Women's Health

Calcium plus Vitamin D Supplementation and the Risk of Fractures

Osteoporosis contributes to more than 300,000 hip fractures annually in the United States. The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women is equivocal.

This was a double blinded, placebo controlled study designed to evaluate the efficacy of calcium and vitamin D supplementation in reducing hip and other fractures. The authors randomly assigned 36,282 post-

menopausal women, aged 50 to 79, to receive 1000mg of calcium carbonate with 400IU of vitamin D daily or placebo. Exclusion criteria included hypercalcemia, renal calculi, corticosteroid use and calcitrol use. Personal supplemental calcium and vitamin D was allowed.

The authors found that hip bone density was 1.06 percent higher in the calcium plus Vitamin D group. Additionally the treatment group had a hazard ratio of 0.88 for hip fractures, 0.90 for spine fractures, and 0.96 for all fractures. Only the bone density difference was statistically significant.

The authors conclude that among healthy postmenopausal women, calcium with vitamin D supple-

mentation resulted in a small, but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones.

Johnson et al, New England Journal of Medicine, February 16, 2006. NEJM 2006;354:669-683

Editors Note: The authors themselves point out a major weakness in this study. Patients were allowed to take their own calcium and vitamin D supplements during the study. I have difficulty drawing conclusions from the data considering this significant weakness in the study design – MSB

Section Editor: Matthew S. Berry, MD, FACP, FAAEP