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ICOSAPENT ETHYL, TRIGLYCERIDES AND CARDIOVASCULAR RISK

Despite appropriate treatment with statins, patients with cardiovascular risk factors maintain a substantial residual cardiovascular risk. In such patients, elevated triglyceride levels serve as an independent marker for an increased risk of ischemic events. As icosapent ethyl has been shown to lower triglyceride levels, this study, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), was designed to determine the effect of this drug on the risk of cardiovascular events.

Subjects were patients who had elevated triglyceride levels despite statin use, were 45 years of age or older with established cardiovascular disease or were 50 years of age or older with diabetes mellitus and at least one additional cardiovascular risk factor. Those patients were randomized to receive either icosapent ethyl, 2g twice per day, or a placebo. The primary efficacy endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or unstable angina. The secondary efficacy endpoint was a composite of significant cardiovascular or cerebrovascular events or death.

Among the 8,179 participants, at a median follow up of 4.9 years, the median change triglyceride levels were an 18.3% decrease in the treatment group and a 2.2% increase in the control group. A primary efficacy endpoint was documented in 17.2% of the patients in the treatment group and 22% in the placebo group ($p < 0.001$). A key, secondary efficacy event occurred in 11.2% of the treatment group and 14.8% of the placebo group ($p < 0.001$). Of note, baseline triglyceride levels had no influence on the primary or key secondary efficacy endpoints. Significant adverse events did not differ significantly between groups.

Conclusion: This multi-national study of patients with cardiovascular risk factors, all with elevated triglyceride levels despite statin use, found that icosapent ethyl significantly reduced the risk of cardiovascular and major ischemic events.

Bhatt, D., et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med.* 2019, January 3; 380(1): 11-22.

LOWER EXTREMITY INJURY ON SYNTHETIC VERSUS NATURAL TURF

Grass turf has been shown to allow the release of the cleat from the surface at higher forces. This is thought to be a protection against certain injuries. Synthetic turf does not have this capacity. This study compared the injury rates between athletes who compete on synthetic turf and those who compete on natural turf.

Injury data were collected prospectively by medical staff for all 32 teams in the National Football League. Data for injuries of the lower extremities were compared between those which occurred on fields with natural surfaces and those which occurred on fields with synthetic surfaces. These data were reviewed for five seasons. Data was collected for 1,280 games, 555 which occurred on synthetic surfaces and 725 which occurred on natural surfaces.

For total injuries, play on synthetic turf resulted in a 16% higher rate of injuries as compared to natural turf. When the analysis was restricted to noncontact/surface contact injuries, the hazard ratios of synthetic surface/natural surface were 1.46 for knee injuries and 1.68 for ankle/foot injuries.

Conclusion: This study of National Football League athletes found higher rates of injuries to the lower extremity when competing on

synthetic turf than when playing on natural turf.

Mack, C., et al. Higher Rates of Lower Extremity Injury on Synthetic Turf Compared with Natural Turf among National Football League Athletes. Epidemiologic Confirmation of a Biomechanical Hypothesis. *Am J Sports Med.* 2019, January; 47 (1): 189-196.

MELATONIN FOR TRAUMATIC BRAIN INJURY

After a traumatic brain injury (TBI), a complex cascade of processes often results in further significant (secondary) brain injury. As previous studies have suggested that melatonin may have neuroprotective qualities, this literature review and meta-analysis explored the efficacy of melatonin for the treatment of acute TBI.

A literature review was completed for randomized, placebo-controlled trials involving patients with TBI treated with melatonin. From the review, eight articles were identified which had information suitable for a meta-analysis. The range of the melatonin dose was 0.625 mg/kg to 200 mg/kg, although the most frequent dose was 5 mg/kg.

Data revealed that melatonin decreased acute contusion volume by a standardized mean difference (SMD) of 2.22, decreased cerebral edema by a SMD of 1.91 and had a favorable effect on neurological status by a SMD of 1.35. In addition, those taking melatonin had an improved performance in cognitive tasks, by a SMD 1.16, and demonstrated improved memory by a SMD of 1.16. The overall outcome when effects were combined was a SMD of 1.51.

Conclusion: This literature review and meta-analysis, including data from animal studies, concerning acute brain injury, suggests that melatonin may have a protective

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effect on behavioral and pathological outcomes.

Barlow, K., et al. Melatonin as a Treatment after Traumatic Brain Injury: A Systematic Review and Meta-Analysis of the Pre-Clinical and Clinical Literature. **J Neurotrauma**. 2019, February; 36 (4):523-537.

WHOLE BODY CRYOTHERAPY FOR FIBROMYALGIA

Fibromyalgia (FM) is a prevalent and disabling disease with unclear pathology, and few effective treatments. Whole body cryotherapy (WBC) has been shown to decrease inflammation and produce analgesia, with positive effects reported for patients with rheumatoid arthritis and ankylosing spondylitis. This study explored the effect of WBC as a treatment for FM.

This randomized, crossover, clinical trial, included patients 25 to 80 years of age with FM for at least one year, all unresponsive to treatment attempts. Those randomized to a treatment arm underwent WBC treatment on alternating days for three weeks. Each session included three minutes in a cabin with temperatures reduced to -196°C. The groups then reversed. The primary outcome measures were a ten-point visual analog scale (VAS) for pain and the FM impact questionnaire (FIQ). Secondary endpoints included disease severity, assessed by the combined Index of Severity of Fibromyalgia (ICAF) and the SF-36.

After the treatment sessions were completed the mean improvements in VAS scores were three in the WBC group and 0.3 in the control group. ($p < 0.001$). In addition, better improvement was found in the WBC group in improvement in scores on the FIQ ($p < 0.001$) and the ICAF ($p < 0.001$). Five patients reported mild adverse events during WBC, notably during the first session, all of which waned in subsequent sessions.

Conclusion: This study of patients with recalcitrant fibromyalgia found that three-minute sessions of cryotherapy every other day for three weeks resulted in significant improvements in pain scores and fibromyalgia impact scores.

Rivera, J., et. Al. The Effect of Cryotherapy on Fibromyalgia: A Randomized, Clinical Trial Carried Out in a Cryosauna Cabin. **Rheum**

Intern. 2018, December; 38(12): 2243-2250.

SODIUM HYALURONATE AND PLATELET RICH PLASMA FOR ROTATOR CUFF TEARS

The treatment of partial thickness rotator cuff tears can include conservative and surgical interventions. Among the nonsurgical outcomes, sodium hyaluronate (SH) and platelet rich plasma (PRP) are relatively new. This study investigated the effects of SH combined with PRP for the treatment of partial thickness rotator cuff tears.

Subjects were 184 patients, 18 to 55 years of age, diagnosed with partial thickness rotator cuff tears, confirmed by magnetic resonance imaging. The participants were randomized to receive normal saline (4 mL), SH (4 mL), PRP (4 mL) or SH plus PRP (2mL +2mL), injected once per week for four weeks. The primary outcome measure was the Constant score. Secondary measures included the American Shoulder and Elbow Surgeons (ASES) and the VAS pain scores.

At one and three months, compared with the control group, the Constant and ASES scores were significantly improved in the SH and the SH+PRP groups. At one month, VAS pain scores were significantly lower in the SH and SH+PRP groups than in the normal saline and PRP groups. At six and 12 months, VAS score improvements were best in the SH+PRP group. At one year, compared with the other groups, the SH+PRP group showed the most improvement in the Constant, VAS and ASES scores, and rotator cuff tear size.

Conclusion: This study found that PRP can enhance the recovery of small to medium partial thickness rotator cuff tears, with better improvement when combined with sodium hyaluronate.

Cai, Y., et al. Sodium Hyaluronate and Platelet Rich Plasma for Partial Thickness Rotator Cuff Tears. **Med Sci Sports Exerc**. 2019, February; 51 (2): 227-233.

INTERLEUKIN-1 RECEPTOR ANTAGONIST FOR TENDINOPATHY

The cytokine, interleukin-1 (IL1), has been found in elevated levels in

patients with tendinopathy. This study was designed to determine whether Anakinra, an IL1 receptor antagonist (IL1 RA), can effectively treat tendinopathy.

This animal study included 48, female, Sprague Dawley rats, all exposed to carrageenan (CAR), a reproducible means of developing inflammation. The animals were randomized to one of three groups, a control group (CON), a CAR group or a CAR plus Anakinra group (CAR+A). The CON group received 0.1 mL saline for six weeks. The intervention groups were treated with carrageenan for four weeks. Beginning at week three, the CAR+A group received Anakinra at 2.5 mg/kg added to the carrageenan and 0.94 mg of the carrageenan alone for the final two weeks, while the CAR group received saline for the final two weeks.

The CAR+A group demonstrated fewer plaque-like lesions than did the CAR group. In addition, the CAR group demonstrated shorter tendon lengths than the other two groups ($p < 0.05$ for both). The CAR group demonstrated significantly greater histologic changes than did the CAR+A group. For all histologic factors studied, more pathology was noted in the CAR than in the CAR+A group ($p < 0.05$). The tensile loads did not differ between the three groups.

Conclusion: This animal study of tendinopathy found that an antagonist to the IL1 receptor may reduce pathological signs of tendinopathy.

Eskildsen, S., et al. The Use of an IL1 Receptor Antagonist to Reverse the Changes Associated with Established Tendinopathy in a Rat Model. **Scand J Med Sci Sports**. 2019, January; 29 (1): 82-88.

CLOPIDOGREL PLUS ASPIRIN VERSUS ASPIRIN FOR TIA OR MINOR STROKE

Clinical studies have demonstrated that patients who experience minor ischemic stroke or transient ischemic attacks (TIA) benefit from antiplatelet therapy. The Clopidogrel In High Risk Patients with Acute Nondisabling Cerebrovascular Event (CHANCE) trial found that adding Clopidogrel to aspirin within 24 hours of a minor stroke or TIA and continuing for 21 days can reduce the risk of stroke without increasing the risk of hemorrhage. The Platelet-Oriented Inhibition in New TIA and

Minor Ischemic Stroke (POINT) study found a 20% reduction in the hazard of stroke with this combination. This literature review and meta-analysis further explored this issue.

After a literature review, studies were selected involving a total of 10,447 participants. All studies involved intervention within 12 to 24 hours after symptom onset. The pooled analysis found that dual antiplatelet therapy within 24 hours of symptom onset reduced the risk of nonfatal recurrent stroke (relative risk 0.70). There was no apparent impact on all-cause mortality. The meta-analysis indicated that the combination use within 24 hours of symptom onset resulted in a relative risk reduction of 30%, and an absolute risk reduction of 1.9%, for recurrent ischemic stroke within 90 days.

Conclusion: This literature review and meta-analysis found that dual antiplatelet therapy within 24 hours of a high-risk TIA or minor stroke, and continuing for 21 days, significantly reduces the risk of a subsequent stroke.

Hao, Q., et al. Clopidogrel Plus Aspirin versus Aspirin Alone for Acute Minor Ischaemic Stroke or High Risk Transient Ischaemic Attack: Systematic Review and Meta-Analysis. **BMJ**: 2018;364: K5108.

CILOSTAZOL AND DELAYED CEREBRAL ISCHEMIA

Delayed cerebral ischemia (DCI) is the major cause of death and disability among patients with an aneurysmal subarachnoid hemorrhage (aSAH). The concept of DCI has evolved from an etiology of vasospasm to other complementary factors, including spreading depolarization (SD). As the antiplatelet drug, cilostazol, a selective inhibitor of phosphodiesterase3, has been found to have some beneficial effects on DCI, this study assessed the effect of this medication on SD after aSAH.

Subjects were 74 patients admitted with an anterior circulation aSAH repaired by clipping within 72 hours. The patients were randomized to receive either a placebo or cilostazol, 100 mg twice per day, for 12 days. DCI was defined as the development of new focal neurologic signs or a deterioration in the level of consciousness by at least two points on the Glasgow Coma Scale (GCS)

score. Baseline digital subtraction angiography and/or CT angiography was performed at admission, with follow-up CTs at 7, 14, 30 and 90 days. In addition, an animal model of SAH was used to assess the effect of cilostazol on perfusion deficits.

At follow-up, DCI was detected in 13% of the treatment group and in 40% of the control group ($p = 0.08$). A new infarction was noted in 8.7% of the treatment group and in 24% of the control group. In addition, DCI was detected in 13% of the treatment group and in 40% of the control group ($p = 0.036$). After adjusting for age, this difference failed to reach significance ($p = 0.084$). At six months, poor outcome, as measured by the GOS was found in 26% of the treatment group and in 40% of the control group. In the animal studies, the cilostazol group had a reduction in the duration in spreading ischemia ($p = 0.02$).

Conclusion: This prospective study of patients with aneurysmal subarachnoid hemorrhage found that cilostazol may be able to decrease the risk of subsequent infarctions, corresponding to a trend towards less DCI.

Sugimoto, K., et al. Cilostazol Decreases Duration of Spreading Depolarization and Spreading Ischemia after Aneurysmal Subarachnoid Hemorrhage. **Ann Neurol**. 2018, Dec; 84(6): 873-885.

HEALTH BEHAVIORS AFTER STROKE

In 2010, the American Heart Association (AHA) defined ideal cardiovascular health according to seven metrics known as Life's Simple Seven (LS7). These metrics included health behaviors (not smoking, maintaining a healthy body mass index (BMI), engaging in physical activity and eating a healthy diet), as well as health factors (control of blood pressure, total serum cholesterol and blood glucose). This study examined the trends in LS7 among survivors of stroke.

Data from the National Health and Nutrition Examination Surveys (NHANES) III (1988 to 1994) and the continuous NHANES (1999 to 2014) were analyzed. A health metric score was calculated (range, zero=worst to 7=best) by adding one point for every ideal metric met. Participants were categorized as low (zero to one), medium (two to three) or high (four or

more) in compliance with LS7 metrics.

Of the 1,597 participants, the proportion with low LS7 scores increased from 17.9% in 1988 to 1994 to 35.4% in 2011 to 2014 ($p<0.001$). Over that time frame, the prevalence of poor blood pressure ($\geq 140/90$ mm Hg) and poor cholesterol (≥ 240 mg/dL) decreased, while the prevalence of poor body mass index (≥ 30 kg/m²), poor diet (healthy eating index score <50) and poor physical activity (zero minutes of moderate/vigorous activity per week) increased ($p<0.05$ for all comparisons). The prevalence of poor physical activity increased from 44.6% to 70.9% ($p<0.001$), and that of poor diet increased from 14.2% to 50.6%.

Conclusion: This study found that, since 1988, among stroke survivors, the rates of elevated blood pressure and poor lipid control have decreased, but the rates of obesity, poor diet and physical inactivity increased.

Lin, A., et al. Less than Ideal: Trends in Cardiovascular Health among U.S. Stroke Survivors. **Stroke**. 2019, January; 50(5): 5-12.

STATIN USE AND HEMORRHAGIC STROKES

Studies have demonstrated the benefits of statins in reducing the risk of primary stroke and cardiovascular events. However, the benefits of these medications for secondary stroke prevention have been controversial, particularly in patients with previous hemorrhagic stroke. This systematic review and meta-analysis were designed to better understand the effect of statin use for patients with ischemic stroke (IS) and hemorrhagic strokes.

This analysis included comparative studies of patients receiving statins versus control (placebo or no treatment), after a previous intracranial hemorrhagic (ICH) or IS. The primary outcome variable was ICH and secondary outcomes included IS, any stroke, all-cause mortality and functional outcome. Pooled, binary event data were compared using risk ratios (RR).

In patients with prior ICH, recurrent ICH in those treated with a statin was similar to that of controls (RR 1.04). A significant reduction in all-cause mortality was found among those treated with statins ($p<0.001$;

RR 0.49). Among those with previous ICH, poor functional outcome was reduced more among the statin users than among the control group ($p<0.001$). In patients with prior IS, a reduction in the risk of any stroke was noted with the use of statins ($p=0.04$), with no significant increase in ICH. However, patients who underwent thrombolysis after an IS had an insignificant increase in the risk of ICH with statins, as compared to those without thrombolysis.

Conclusion: This meta-analysis found that patients with previous ischemic or hemorrhagic stroke did not have an increased risk of ICH with the use of statins, and had improved mortality and functional outcomes.

Ziff, O., et al. Statins and the Risk of Intracerebral Haemorrhage in Patients with Stroke: Systematic Review and Meta-Analysis. **J Neurol Neurosurg Psychiatry**. 2019, January; 90(1): 75-83.

BLOOD FLOW RESTRICTED EXERCISE FOR POWER LIFTERS

For strengthening, the traditional formula involves training with weights greater than 70% of the one-repetition maximum (1RM). However, similar effects have been found with reduced weights using blood flow restriction (BFR). This study assessed the effect of BFR training during six weeks of strengthening by elite power lifters.

A group of power lifters were assessed for their 1RM. The subjects were randomized to a conventional training group or a BFR group. The conventional training group performed front squats at 60 to 85% of their 1RM. The BFR group performed similar training, with BFR sessions inserted at weeks one and three, including four sets at 30% of the 1RM, with a blood pressure cuff at their proximal thigh inflated to 120mmHg. After 6.5 weeks of training, strength was assessed, muscle biopsies taken and US measurements made to determine the myofiber areas (MFA) and cross-sectional area (CSA) of m. rectus femoris (RF), m. vastus lateralis (VL), m. vastus medialis (VM) and m. vastus intermedius (VI).

The BFR exercise (BFRRE) group increased strength in knee extension ($p=0.04$) with no significant change in the conventional group. The difference between groups did not

reach statistical significance. Type I fibers increased more in the BFR group than in the control group ($p=0.003$), with no increase in type II fibers. Muscle thickness (measured as the shortest distance between the upper and lower aponeuroses) was also significantly greater in the BFR group than in the control group for the RF, VL and VM ($p=0.01$, 0.02, and 0.02, respectively). The number of myonuclei in type I fibers increased significantly more in the BFR group than in the control group ($p=0.01$).

Conclusion: This study of elite power lifters is found that adding two blocks of front squats with low load, blood flow restriction exercise resulted in an increased quadriceps cross-sectional area, and a preferential hypertrophy of type I fibers.

Bjornsen, T., et al. Type 1 Muscle Fiber Hypertrophy after Blood Flow Restricted Training in Powerlifters. **Med Sci Sports Exerc**. 2019, February; 51(2): 288-298.

WEEKEND WARRIORS

The United States Federal Physical Activity Guidelines recommend 150 minutes of moderate to vigorous intensity physical activity (MVPA), performed in bouts of at least ten minutes. However, the optimal number of days per week during which to perform this exercise remains unclear. This study examined the effect of activity performed only on weekends.

Subjects were drawn from the National Health and Nutrition Examination Survey (NHANES), including 5,461 adults, >40 years of age. During the study periods of 2003-2004 and 2005-2006, the participants wore accelerometers and calculated the amount of time spent per week in MVPA. Those who spread their activity over the entire week ("regular" R) were compared to those who accrued $\geq 50\%$ of their weekly MVPA on only one or two days ("weekend warriors" WW).

At an average follow-up of 77.4 months, 394 deaths were reported among the original 3,438 participants. An inverse dose response was found for MVPA per week and mortality, both for the R and WW participants. The WW group had mortality rate reductions that were similar to the R group, with superior reductions as compared to the inactive group. After adjusting for relevant covariables,

those who engaged in more than 37.5 minutes of MVPA per week had a 60-69% reduction in mortality rate. In an adjusted analysis, neither the average nor the maximum bout duration were significant predictors of mortality.

Conclusion: This study found that individuals whose exercise occurs mostly on one to two weekend days have similar reductions in mortality compared to those who spread their exercise throughout the week.

Shiroma, E., et al. Physical Activity Patterns and Mortality: The Weekend Warrior and Activity Bouts. **Med Sci Sports Exer.** 2019, January; 51 (1): 35-40.

INJECTABLE CARTILAGE FOR FOCAL CHONDRAL LESION

Among tissue engineering approaches to chondral repair are injectable hydrogels which can form three-dimensional networks. These can be delivered as a liquid solution and then polymerized *in vivo*. This animal study assessed the efficacy of a novel cartilage mimetic hydrogel for the repair of chondral defects.

A hydrogel was constructed, designed to polymerize within minutes. Bone marrow derived mesenchymal stem cells (MSC) were isolated and culture expanded, with those cells then encapsulated in the photopolymerized hydrogel. Ten rabbits underwent bilateral, surgical chondral lesions, with the lesions randomly assigned for treatment with hydrogel (H), hydrogel plus MSCs (H+) or a placebo (P). In the H and H+ groups, 30 to 40 milliliters of polymer solution were injected, and then photopolymerized, using a 405 nm blue light for 40 seconds. At six months, the animals were euthanized for analysis.

At six months, the macroscopic evaluation showed nearly normal tissue repair in the H and H+ groups. The addition of mesenchymal stem cells did not enhance cartilage repair, with some cases suggestive of poorer outcomes. In both hydrogel groups, repaired tissues were scored as a mix of hyaline and fibrocartilage tissue. The H group had the best bonding to adjacent articular cartilage, with better cellularity and defect filling scores.

Conclusion: This animal study demonstrated that a cartilage mimetic hydrogel can be injected and then

polymerized during surgery, with immediate weight bearing, resulting in good defect repair. The addition of mesenchymal stem cells did not enhance the repair.

Pascual-Garrido, C., et al. Photopolymerizable Injectable Cartilage Mimetic Hydrogel for the Treatment of Focal Chondral Lesions. A Proof of Concept Study in a Rabbit Animal Model. **Am J Sport Med.** 2019, January; 47 (1): 212-221.

ESSENTIAL OILS FOR MULTIDRUG RESISTANT BACTERIA

Concern has been expressed about emerging multidrug resistant (MDR) bacteria seen worldwide. As citizens of developing countries often cannot afford modern pharmaceutical drugs, many continue to use indigenous, traditional medicinal plants. This study evaluated the combined antibacterial effect of three Ethiopian essential oils to treat MDR bacteria, *Blepharis cuspidata*, *Boswellia ogadensis* and *Thymus schimper*.

Essential oils were extracted from fresh leaves of each of the three plants using a steam distillation process. The test organisms were MDR strains of *staph aureus*, *Escherichia coli* and *Klebsiella pneumoniae*. The antimicrobial effect of each oil was measured by the minimal inhibitory concentration (MIC). The efficacy of the essential oils was assessed in isolation and when combined.

The MDR bacteria were resistant to the majority of antibiotics tested. The essential oils demonstrated an antibacterial effect against *Escherichia coli* and *Klebsiella pneumoniae*, as well as multidrug resistant strains. The combined essential oils of *B. cuspidata* and *T. schimper* had an MIC of 0.39 µl/ml against MRSA and an MIC value 0.39 – 6.25 µl/ml against MDR *E. coli* and *K. pneumoniae*. Combinations of *B. cuspidata* and *B. ogadensis* had MIC values ranges from 0.78 to 6.25 µl/ml for *E.coli* and *K. pneumoniae* and 1.56 µl/ml for MRSA. The essential oils of *B. cuspidata* had a higher antibacterial effect than did the others.

Conclusion: This study of essential oils derived from Ethiopia found that traditional medicinal plants have an antibacterial effect against *S. aureus*, *E. coli*, and *K. pneumoniae*,

as well as multidrug resistant strains of these species. Their effectiveness varies with concentration, type of essential oil and combinations of these.

Gadisa, E., et al. Combined Antibacterial Effect of Essential Oils from Three Most Commonly Used Ethiopian Traditional Medicinal Plants on Multidrug Resistance Bacteria. **BMC Complement Altern Med.** 2019; 19: 24.

MEDICAID HOSPITAL READMISSION REDUCTION

In the year 2012, seven percent of the United States population was hospitalized, with one in 12 adults readmitted within 30 days. It has been estimated that one fourth of all 30-day hospital readmissions are preventable, with many traceable to inadequate post-discharge follow-up. This study reviewed the effect of a primary care physician follow-up within seven days of discharge on the readmission rates of patients with Medicaid.

This study was conducted in Camden, New Jersey, where Medicaid covers 57% of the residents. This program engaged patients while they were still hospitalized, in order to facilitate a primary care appointment within seven days of discharge. During that visit, the patients were alerted to the benefits of primary care follow-up. Visits were scheduled, transportation offered and a 20-dollar gift card presented after appointment completion. In addition, the primary care practices were offered an enhanced reimbursement of \$100 for visits within 14 days and \$150 for visits within seven days. For each patient involved in the treatment group, five, matched patients were identified for a control group. The groups were compared for rates of rehospitalization within 30 days of discharge.

Between 2014 and 2016, there were 2,580 hospitalizations of adult patients. Of these, 450 discharges were followed by primary care within seven days, and 607 within 14 days. Of the hospitalizations in the intervention group, 12.7% had a readmission within 30 days, as compared with 17.5% among the matched controls ($p=0.03$). At 90 days post-discharge, 28% in the treatment group were readmitted, as

compared with 30.7% in the matched controls ($p=0.002$).

Conclusion: This study of Medicaid recipients found that, after hospitalization, those seen for follow up by a primary care physician within seven days had a significant reduction in 30- and 90-day hospital readmission.

Wiest, D., et al. Outcomes of a Citywide Campaign to Reduce Medicaid Hospital Readmissions with Connection to Primary Care within Seven Days of Hospital Discharge. **JAMA Open.** 2019; January 25;2 (1): 1-10.

DYNAMIC BALANCE AND RISK OF CONCUSSION

After a concussion, athletes are at a higher risk of sustaining a repeat concussion. This study investigated the association between dynamic balance performance and the risk of future concussion.

Subjects were 109, elite, male, rugby union players from four senior Irish teams. All underwent baseline testing sessions and received a single, inertial sensor to wear at the level of the fourth lumbar vertebra to match the body's center of mass. While wearing the sensor, the subjects completed four practice trials and three recorded trials of the pre-defined directions of the Y-balance test (YBT).

Reach distances were normalized to each individual according to leg length. The subjects were followed during the ensuing rugby season, with the incidence of concussions documented. Independent variables included self-reported concussion history, playing position, age group, dynamic balance variables and the entropy of the gyroscope magnitude signal during each YBT excursion.

Of the 109 players, 44 had a history of concussion, with 21 sustaining a concussion in the follow-up season. Those with suboptimal balance at baseline were 2.81 times more likely to sustain a concussion during the following season, even after controlling for concussion history.

Conclusion: This study of professional rugby players found that those with suboptimal balance at baseline had a significantly increased risk of concussion during the following season.

Johnston, W., et al. Association of Dynamic Balance with Sports-Related Concussion: A Prospective, Cohort Study. **Am J Sport Med** 2019, January; 47 (1): 197-205.

ZOLEDRONATE FOR FRACTURE PREVENTION IN OLDER WOMEN

Bisphosphonates are the primary class of medication used to prevent osteoporotic fractures. However, the evidence for their effects in patients with osteopenia is lacking. Zoledronate can be administered at intervals of one year or longer, and is preferred over oral bisphosphonates by the majority of women. This study assessed the effects of zoledronate on the risk of fractures in postmenopausal women with osteopenia.

Subjects were ambulatory, postmenopausal women, 65 years of age or older, all with osteopenia confirmed by bone mineral density studies. The women were randomized to receive four infusions of either alendronate, 5 mg, or normal saline, at 18-month intervals. All subjects received cholecalciferol, 1.25 mg per month, for the duration of the trial. The primary endpoint was the time to first fragility fracture.

During follow-up, a fragility fracture was diagnosed in 190 women in the placebo group and 122 in the treatment group ($p<0.0001$). Secondary endpoints were also better in the treatment group including symptomatic fractures, [Hazard Ratio (HR) 0.73], death (HR 0.65) and cancer (HR 0.67).

Conclusion: This study of postmenopausal women with osteopenia found that administration of zoledronate every 18 months for six years reduces the risk of fragility fractures, death and cancer.

Reid, I., et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. **N Engl J Med.** 2018, December 20; 379(25): 2407-2416.

MARINE N-3 FATTY ACIDS, CARDIAC DISEASE, AND CANCER

Studies of the effect of N-3 fatty acid supplements on clinical cardiovascular outcomes have shown inconsistent results. This study, the vitamin D and omega-3 trial (VITAL), was conducted to better understand the effect of those supplements.

This randomized, double-blind, placebo-controlled trial included men, 50 years of age or older, and women, 55 years of age or older. The subjects were randomized to receive a placebo, with either vitamin D3 at a dose of 2,000 international units per day or N-3 fatty acids at 1 g per day, 2 placebos, or both active agents. At baseline, questionnaires were used to collect information regarding clinical and lifestyle risk factors, including a dietary questionnaire. The primary endpoints were major cardiovascular events and invasive cancer of any type.

Subjects were 25,871 adults of whom 16,956 underwent blood sampling. At a median 5.3 year follow up 805 major cardiovascular events occurred, including 386 in the N-3 group and 419 in the placebo group ($p=0.24$). In addition, invasive cancers were identified in 820 of the N-3 group and 797 of the placebo group ($p=0.56$).

Conclusion: This primary prevention trial did not find that supplementation with N-3 fatty acids or with vitamin D3 reduces the incidence of major cardiovascular events or invasive cancer.

Manson, J., et al. Marine N-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. **N Engl J Med.** 2019; January 380: 23-32.

ENGINEERED GLOVE TO DETECT RADIOLOGICALLY ISOLATED SYNDROME

A glove engineered to measure motor performance of the fingers has been shown to discriminate individuals with early-stage multiple sclerosis (MS) from healthy controls. This study assessed whether this glove could be useful in diagnosing individuals with radiographically isolated syndrome (RIS), who are asymptomatic with MRI findings suggestive of MS.

Subjects were 17 adults with a diagnosis of RIS and the presence of white matter lesions, all with no previous remitting clinical symptoms. A control group included 17 age and gender matched, healthy controls. All participants were asked to perform a bilateral repetitive finger to thumb opposition sequence at maximum velocity, and then at two Hz, while paced by a metronome. All underwent brain MRI examination on the day of the glove experiment.

Outcome measures were maximum velocity and coordination of movement between the hands.

Compared to that of healthy controls, the rate of maximum velocity in patients with RIS was lower ($p=0.005$). In addition, the hand movements were less synchronized in the RIS group ($p=0.006$).

Conclusion: This study of patients with asymptomatic radiologically isolated syndrome found that finger motor performance and bimanual coordination impairment could be detected with an engineered glove.

Bonzano, L., et al. Subclinical Motor Impairment Assessed with an Engineered Glove Correlates with Magnetic Resonance Imaging Tissue Damage in Radiologically Isolated Syndrome. *Europ J Neurol*. 2019; 26(1): 162-167.

GRANULOCYTE COLONY STIMULATING FACTOR FOR SPINAL CORD INJURY

For patients who have a traumatic spinal cord injury (tSCI), secondary mechanisms unfold in different phases, which can result in further clinical damage. Among the targets for blocking this secondary cascade, granulocyte colony stimulating factor (G-CSF) has been studied for its potential neuroprotective effect. This prospective, placebo-controlled trial assessed the neurologic effects of G-CSF among patients with incomplete tSCI.

Subjects were between 18 and 60 years of age, all with an incomplete (tSCI) of between one- and six-months' duration. The participants were randomized to receive seven daily injections of either placebo ($n=26$) or 300 micrograms of G-CSF ($n=28$). A neurologic evaluation was made at baseline and at follow-up, using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), with other measures including the American Spinal Injury Association (ASIA) and the International Association of Neurorestoration Spinal Cord Injury Functional Rating Scale (IANR-SCIFRS) and the Spinal Cord Independence Measure III (SCIM-III) for assessment of impairment.

After six months, the AIS grade remained unchanged in the placebo group, with 11 patients improving by at least one grade in the treatment group. The mean changes in the

ISNCSCI motor scores were 14.9 points in the treatment group and 1.4 points in the placebo group ($p<0.001$). Compared with the treatment group, IANR-SCIFRS functional scores were significantly better in the treatment group ($p<0.001$). Increased neuropathic pain was experienced in 10.7% of the treatment group, with 7.1% demonstrating increased spasticity.

Conclusion: This study of patients with incomplete spinal cord injury found that seven daily injections of 300 micrograms of G-CSF can significantly improve motor and sensory function.

Derakhshanrad, N., et al. Subcutaneous Granulocyte Colony Stimulating Factor Administration for Subacute Traumatic Spinal Cord Injuries, Report of Neurological and Functional Outcomes: A Double-Blind, Randomized, Controlled, Clinical Trial. *J Neurosurg Spine*. 2019, January; 30(1): 19-30.

FUNCTIONAL CONNECTIVITY THROUGH MUSIC IN ALZHEIMER'S

Studies have shown a beneficial effect of music therapy for patients with Alzheimer's disease (AD). Recent studies have discovered an area of the brain, important for music recognition, that is relatively preserved in patients with AD. This study reviewed the cognitive effects of favored music on patients with AD-related dementia.

Subjects were 17 adult patients with a clinical diagnosis of AD-related dementia. All were studied with functional MRI before and after exposure to a personalized music program.

After listening to that program, the patients demonstrated activation of the supplementary motor area, an area associated with memory for familiar music. In addition, increases in functional connectivity were found in corticocortical and corticocerebellar networks.

Conclusion: This study of adult patients with Alzheimer's disease found that, when exposed to preferred music, activation of the supplementary motor area occurred, corresponding to a widespread increase in functional connectivity.

King, J., et al. Increased Functional Connectivity after Listening to Favored Music in Adults with

Alzheimer's Disease. *J Prev Alzheimers Dis*. 2019; 6(1): 56-62.

IMPACT LOCATION AND BRAIN STRAIN

While the prevalence of concussion is not clearly understood, estimates ranged between 1.6 and 3.8 million sports related concussions in United States each year. This study compared the relationship between the impact magnitude and direction to the subsequent variation of strain levels in regions of the brain.

Using a model of the human head and brain, linear acceleration was recorded using an accelerometer, while rotational velocity was measured using a three-axis gyroscope. Twelve tests were conducted with constant energy impacts ranging from 20g to 200 g. These impacts were provided from the frontal, lateral and rear direction. Strains and pressures were measured at various portions of the brain, and compared by direction of impact.

The effect of the impact on different regions of the brain varied by direction of the impact. Both angular and linear accelerations were higher in lateral and rear impacts as compared to frontal impacts. With the acceleration profile held constant, frontal impact produced the highest strains in the midbrain as compared to other regions of the brain. In contrast, strains in the corpus callosum were greatest when the impact was from a lateral direction.

Conclusion: This study, modeling the human brain, found that angular accelerations are up to 30% higher in lateral and rear impacts as compared to frontal impacts. Frontal impacts seem more likely to damage the midbrain while lateral impacts are more likely to impact the corpus callosum.

Tiernan, S et al. The Effect of Impact Location on Brain Strain. *Brain Inj*. 2019;10.1080/02699052.

DIRECT CURRENT STIMULATION AND EXERCISE PERFORMANCE

Previous studies have suggested that transcranial direct current stimulation (tDCS) may enhance performance in sports. This literature review and meta-analysis was completed to better understand the effect of this intervention on sports

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*Amy Unwin, M.D.
Anna Coles, M.D.
Ashley Eaves, M.D.
David Niumatalolo, M.D.
University of Washington, Seattle, WA

*Bonnie Weigert, M.D.
Matthew J. Cowling, D.O.
University of Wisconsin, Madison, WI

*Sean Hoge, M.D.
*Timur Korshin, M.D.
Harnek Singh Bajaj, M.D.
VCU, Richmond, VA

*Michael Sookchoff, M.D.
Michael Bonnette, M.D.
Sam Park, M.D.
Dan Probst, M.D.
Washington U, St. Louis, MO

Executive Editor Emeritus
Donald F. Langenbeck, Jr., M.D.

Subscription Manager
Michael P. Burke, M.S.

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performance.

A literature search was completed using multiple databases, for studies including tDCS and exercise, sport or physical performance. From the search, 24 studies were identified for use in the analysis.

Data were available for 386 participants with 63% of the studies assessing stimulation on a single muscle group while 37% studied the effect on whole body exercise. The overall effect of tDCS on performance was found to be significant ($p=0.001$). In addition, anodal tDCS was found to have a small but positive effect on performance ($p=0.0012$).

Conclusion: This meta-analysis found that transcranial direct current stimulation may have a positive effect on exercise performance though the effect was found to be small.

Holgado, D et al. The Effects of Transcranial Direct Current Stimulation on Objective and Subjective Indexes of Exercise Performance: A Systematic Review and Meta-Analysis. **Brain Stimul.** 2019, January;12:242-250.

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