

REHAB IN REVIEW

TM

WWW.REHABINREVIEW.COM

Volume 28 Number 3

Published by Physicians
In Physical Medicine and Rehabilitation

March 5, 2020

POLYNUCLEOTIDES AND HYALURONIC ACID KNEE INJECTIONS

Hyaluronic acid (HA) is a natural component of soft connective tissue with the ability to restore the viscoelastic properties of the synovial fluid (SF) and joint lubrication. It also has antiapoptotic, anti-inflammatory, antiangiogenic, and antifibrotic properties. In addition, polynucleotides (PNs) are a mixture of purines, pyrimidines, and deoxyribonucleosides, which have shown positive results in musculoskeletal tissue regeneration. This study compared the efficacy of intraarticular knee injections with PNs mixed with HA (PNHA) to that of HA alone.

This study included 100 patients with a diagnosis of knee OA. Patients were randomized to receive injections of the knees with PNs (10 mg/mL) of controlled natural origin (fish sperm) and 10 mg/mL of an HA of biotechnological origin, with a total content of active ingredients of 40 mg in two mL. Subjects received injections of two mL of PNHA or HA every week for a total of three injections. At baseline and up to five months from the first treatment clinical function and pain were measured by the WOMAC score and the Knee Society Score (KSS). Biochemical and immunoenzymatic analysis were performed at baseline and at two weeks.

The KSS total scores showed significantly better results in the PNHA group compared with HA at follow up weeks three and four ($p < 0.05$) and at week five ($p = 0.009$). No significant differences were observed for the WOMAC score between groups during the follow-up. The biochemical evaluation showed that synovial fluids of all the patients were normal for color, clarity, and density (mucin clot test).

Conclusions: These findings suggest that a joint injection with PNs, in combination with HA, is more effective in improving knee function

and pain, in a joint affected by OA, compared with HA alone.

Dallari, D., et al. Efficacy of Intra-Articular Polynucleotides Associated with Hyaluronic Acid Versus Hyaluronic Acid Alone in the Treatment of Knee Osteoarthritis: A Randomized, Double-Blind, Controlled Clinical Trial. *Clin J Sport Med.* 2020, January; 30(1):1-7.

LOW-DENSITY LIPOPROTEIN TARGETS AFTER ISCHEMIC STROKE

The Stroke Prevention by Aggressive Reduction in Cholesterol Level (SPARCL) trial established the basis for recommendations of intensive therapy to lower serum lipid levels after a transient ischemic attack (TIA) or ischemic stroke (IS). There was, however, no target low density lipoprotein (LDL) level in these recommendations. This study compared the outcomes of patients with a target level of LDL cholesterol < 70 mg/dL to those of patients with a higher target range of 90 to 100 mg/dL.

Subjects were adult patients who had sustained an ischemic stroke within the past three months, all with a modified Rankin Scale score of zero to three. The participants were randomized to a target LDL cholesterol of less than 70 mg/dL or a target range of 90 to 100 mg/dL. Investigators were allowed to prescribe any type and dose of statin to reach these targets. The composite primary endpoint was major cardiovascular events.

At a median follow-up of 3.5 years, the mean LDL cholesterol levels were 65 mg/dL in the lower target group and 96 mg/dL in the higher target group. The primary endpoint occurred in 0.5% of the lower target group and in 10.9% of the higher target group (Hazard Ratio 0.78; $p=0.04$). The majority of the endpoint events were cerebral infarctions or strokes of undetermined origin.

Conclusion: This study involving patients with recent ischemic stroke or transient ischemic attack, found that those assigned a target low density lipoprotein cholesterol of less than 70 mg/dL had fewer major cardiovascular events than did those with a target of 90-110 mg/dL.

Amarenco, P., et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. *N Engl J Med.* 2020, January 2; 382 (1): 9-19.

APOE AND DEMENTIA BEFORE AND AFTER A STROKE

Studies have shown that the lipoprotein, APOE, located on chromosome 19, has an isoform with neuropathological effects on neurons, the blood brain barrier and blood vessels. This study reviewed the effect of this allele on the risk of dementia after a transient ischemic attack (TIA) or a stroke.

Subjects were consecutive patients with TIA or stroke who were prospectively recruited from April 1, 2002 to March 31, 2012. Data were collected as part of a population-based cohort study of all acute vascular events occurring within a defined population of 92,728. Data, including education and vascular risk factors, were collected by interview. Premorbid functional status was assessed using modified Rankin and Barthel scores. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). All participants were evaluated by brain imaging. Follow up for cognitive evaluation occurred at one and six months and at one and five years. Genotyping was used to determine the six APOE genotypes ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ types). Genotypes were compared with outcomes.

Of the 1,767 patients tested 1,058 (59.9%) were APOE- $\epsilon 3/\epsilon 3$, 403 (22.8%) were $\epsilon 4/\epsilon 3$, and 30 (1.7%) were $\epsilon 4/\epsilon 4$ types. Compared with APOE- $\epsilon 3/\epsilon 3$ group, the APOE- $\epsilon 4/\epsilon 4$ group had an increased risk of pre-

Editor-in-Chief

David T. Burke, M.D., M.A.
Emory University, Atlanta, GA

Executive Editor

Randolph L. Roig, M.D.
Emory University, Atlanta, GA

Copy Editor

Roberta Alysoun Bell, Ph.D.
Emory University, Atlanta, GA

Assistant Copy Editor

Tracie McCargo
Emory University, Atlanta, GA

Contributing Editors

*Benjamin Sirutis, M.D.
Dhruvil Brahmhatt, M.D.
Joshua Elkin, M.D.
Bassem Hanalla, M.D.
Giorgio A. Negron, M.D.
Kelly Purcell, M.D.
Parth Vyasa, M.D.
Emory University, Atlanta, GA

*Michael Harbus, M.D.
Lissa Hewan-Lowe, M.D.
Icahn Sch. of Med at Mt. Sinai, N.Y., NY

*Sony Issac, M.D.
Parini Patel, D.O.
Nassau Univ., East Meadow, NY

*Alexander Sheng, M.D.
Stephen Leb, M.D.
Ryan Nussbaum, D.O.
Punit Patel, D.O.
N.W.U. /R.I.C., Chicago, IL

*Rosa Pasculli, M.D.
*Perry Zelinger, M.D.
Haruki Ishii, M.D.
Shawn Jacobs, M.D.
Navi Plaha, M.D.
NYU/Rusk Inst., New York, NY

*Michael Gallaher, M.D.
Marielle Araujo, M.D.
Nikhil Potpally, M.D.
Lena Sheorey, M.D.
Rutgers NJMS, Newark, NJ

*Kevin Machino, D.O.
Monica Branch, M.D.
Schwab Rehab Hospital, Chicago, IL

*Roshan Chhatlani, D.O.
Sonny Ahluwalia, D.O.
Jonathan Chapekis, D.O.
Clarisse San Juan, M.D.
Eytan Rosenbloom, DO.
Suny Downstate, Brooklyn, NY

*Ryan Hafner, M.D.
Mia Song, D.O.
Temple University, Philadelphia, PA

*Valerie Chavez, M.D.
Fady Boutros, M.D.
Greg Doornink, M.D.
Tyler Doornink D.O.
Kyaw Lin, D.O.
Blessing Tin Win, M.D.
University of California/Irvine, CA

event dementia ($p=0.004$). An adjusted model revealed that APOE $\epsilon 4/\epsilon 4$ was also strongly associated with post-event dementia at five-years' follow-up ($p=0.001$).

Conclusion: This study of patients presenting with a transient ischemic attack or stroke found that those with who were homozygous with the APOE- $\epsilon 4$ allele had a greater likelihood of pre and post event dementia, as compared to those with other APOE allele combinations.

Pendlebury, S., et al. APOE- $\epsilon 4$ Genotype and Dementia before and after Transient Ischemic Attack and Stroke: Population-Based Cohort Study. *Stroke*. 2020, March; 51:751-758.

METHYLPHENIDATE FOR MENTAL FATIGUE AFTER MILD TRAUMATIC BRAIN INJURY

The most widely used drug for cognitive impairments after traumatic brain injury (TBI) is methylphenidate. This study evaluated the long-term efficacy and safety of this medication for the treatment of mild TBI.

Subjects were patients with mild TBI with post-concussive syndrome for more than six months. Those who were treated with methylphenidate received treatment for a mean of 5.5 years. At baseline and follow up the patients were assessed for depression with the Mental Fatigue Scale (MFS), and for anxiety with the Comprehensive Psychopathological Rating Scale (CPRS). Cognitive function was assessed, including information processing speed with the Digit Symbol Coding (DSC) subtest and the Trail Making Test (TMT) as well as working memory, assessed with the Digit Span (DS) subtest.

A two-way within-subjects analysis of variance found significant interactions with large positive effects with methylphenidate use for fatigue, depression and anxiety. During a four-week withdrawal, a significant deterioration was noted in mental fatigue ($p<0.0001$), depression ($p=0.004$), and anxiety ($p=0.0001$) along with slower processing speed ($p=0.002$).

Conclusion: This study of patients with mild traumatic brain injury found that, at a mean of 5.5 years follow-up, the use of methylphenidate remained associated with improved mental fatigue, depression, anxiety and processing speed.

Johansson, B., et al. Follow-Up after 5.5 Years of Treatment with Methylphenidate for Mental Fatigue and Cognitive Function after a Mild Traumatic Brain Injury. *Brain Injury*.2020; 34(2): 229–235.

SLEEP DISORDER AND CONCUSSION IN ATHLETES

Baseline testing is often employed as representative preinjury performance after sports related concussions. As sleep disorders effect cognitive performance, this study investigated the effect of sleep disorders on baseline measures of concussion.

This study involved 333 student athletes with a previously diagnosed sleep disorder, matched by age, gender, sport and concussion history with 333 athletes with no sleep disorder diagnosis. All subjects underwent assessments with the Brief Symptom Inventory–18 (BSI-18), the Balance Error Scoring System (BESS), the Immediate Post-Concussion Assessment And Cognitive Testing (ImPACT) measure, the Post-Concussion Symptom Scale (PCSS), the Sport Concussion Assessment Tool–Fifth Edition (SCAT-5), and the Standardized Assessment Of Concussion (SAC). Scores on these tests were compared between groups. In addition, test scores were compared by total sleep during the night before testing.

A one way analysis of covariance revealed significantly worse performance in the sleep disordered group on the BESS ($p<0.01$), the BSI-18 Somatization Subtest ($p<0.01$), the BSI–18 Depression Subtest ($p<0.01$), and Anxiety Subtests ($p<0.01$), the Global Severity Index ($p<0.01$), the PCSS ($p<0.01$), the SCAT-5 Symptom Number ($p<0.01$), and Symptom Severity ($p<0.01$) scales, and the SAC ($p<0.01$).

Conclusion: This study of college athletes found that those with a history of diagnosed sleep disorders generally reported more symptoms and performed worse on cognitive measures than did those without a history of sleep disorders.

McAllister-Deitrick, J., et al. Effect of Diagnosed Sleep Disorders on Baseline Concussion Symptom, Cognitive, and Balance Assessments in Collegiate Athletes. *Am J Sport Med*. 2020. DOI: 10.1177/0363546520902701.

EMOTIONAL SUPPORT AND RISK OF INCIDENT DEMENTIA

Previous studies have demonstrated that older people who receive more emotional support have better cognitive performance. This prospective study examined the role of providing or receiving emotional support on the risk of incident dementia.

Subjects were >65 years of age chosen from citizens living in Ohsaki City, Japan. A baseline survey was provided, included questions about emotional support, either given or received, as well as social and medical issues associated with dementia. Examples of social support questions are "Do friends or family consult with you when they are in trouble?" (yes/no), and "Do you have someone with whom you can consult with when you are in trouble?" (yes/no). The data were adjusted for sex, age, history of disease, education level, smoking, alcohol consumption, body mass index, time spent walking per day, psychological distress scores, motor function scores, cognitive function scores, instrumental support, and social participation.

Data were completed for 13,636 adults, with an average age of 73.3 years. Compared with participants who did not give emotional support to others, the hazard Ratio (HR) for incident dementia among those who did give emotional support to others was 0.41. This remained significant in the adjusted model (HR 0.61). Compared with participants who did not receive emotional support, the adjusted risk of incident dementia was greater for those who did receive emotional support (HR 1.10). Compared to those who neither gave nor received emotional support, those who received but did not give support had a significantly higher risk of dementia (HR 1.51).

Conclusion: This Japanese study of elderly individuals demonstrates that providing support to others is associated with a reduced risk of incident dementia, while receiving and not giving emotional support to others was associated with an increased risk.

Liu, Y., et al. Emotional Support (Giving or Receiving) and Risk of Incident Dementia: Ohsaki Cohort 2006 Study. *Arch Gerontol Geriatr.* 2020, January-February; 86:10964.

CALCITONIN GENE-RELATED PEPTIDE ANTIBODIES FOR MIGRAINE

Calcitonin gene-related peptide (CGRP) has been found to play an important role in the pathophysiology of migraine via nociceptive mechanisms in the trigeminovascular system. This meta-analysis investigated the efficacy and safety of CGRP monoclonal antibodies (mAbs) for episodic migraine.

A literature review was completed for randomized double-blind placebo-controlled studies of adults with episodic migraine. The primary efficacy outcome measures were the change in the number of monthly migraine days and the change in monthly acute migraine specific medication days. From this review, 11 studies were chosen, including data from 4,402 participants.

After pooling the data, the improvement in monthly migraine days from baseline to endpoint was greater in the CGRP mAbs group compared with placebo ($p < 0.00001$). In addition, the change in monthly acute migraine-specific medication days from baseline to endpoint was significantly greater for the CGRP mAbs group compared to the placebo group ($p < 0.00001$). The number of those who experienced a $\geq 50\%$ reduction in migraine days per month was greater among those receiving CGRP mAbs than among those in the placebo group (RR 1.51; $p < 0.00001$).

Conclusion: This meta-analysis of 11 randomized controlled trials involving adults with episodic migraines found that calcitonin gene related peptide antibodies could reduce the number of monthly migraine days and migraine specific medication days.

Deng, H., et al. Efficacy and Safety of Calcitonin Gene Related Peptide Binding Monoclonal Antibodies for the Preventative Treatment of Episodic Migraine—An Updated Systematic Review and Meta-Analysis. *BMC Neurol.* 2020; 20(1):1-12.

CREATINE AND DEPRESSION

Epidemiologic studies have suggested a potential association between creatine intake and depression. This study used data from the National Health and Nutrition Examination Survey (NHANES) trial to further explore this association.

Data were obtained from the continuous NHANES for the period 2005 to 2012 for adult participants 20

to 85+ years of age. All were assessed with a screening questionnaire for depression, the Patient Health Questionnaire (PHQ-9), with outcomes resulting in three categories of depression. These included mild-to-moderate, moderately severe, and severe. From dietary questionnaires, an estimate was made of daily intake of creatine. Included in the analysis were potentially modifying demographic, socioeconomic and lifestyle factors.

Data were available for 22,692 adult participants. Among these, depression was identified in 10.23 per 100 persons in the lowest quartile of creatine consumption and 5.98 per 100 persons among the highest quartile ($p < 0.0001$). A protective association between dietary creatine intake and depression was found among women (odds ratio 0.62) and men (odds ratio 0.72) though the findings on men did not reach statistical significance. The relationship was not significant among those taking antidepressant medications. Across the sample, dietary creatine was protective against depression among participants in the third ($p = 0.04$) and fourth ($p = 0.005$) quartiles of creatine consumption relative to the first quartile.

Conclusion: This study, using data from the National Health and Nutrition Examination Survey, found a significant correlation between increased levels of dietary creatine intake and lower rates of depression.

Bakian, A., et al. Dietary Creatine Intake and Depression Risk Among US Adults. *Transl Psychiatry.* 2020, February; 10 (52).

STELLATE GANGLION BLOCK AND POST-TRAUMATIC STRESS DISORDER

Stellate ganglion block (SGB) has been used to treat sympathetically mediated pain conditions since the 1940s. Studies have shown that this procedure may have beneficial effects for those with post-traumatic stress disorder (PTSD), although the data has been inconsistent. This randomized controlled trial was designed to clarify the efficacy of this procedure for patients with PTSD.

Subjects were military personnel with a PTSD Checklist-Civilian Version *DSM-IV* (PCL-C-IV) score of 32 or greater. The participants were assessed at baseline with the PTSD Scale for *DSM-5* (CAPS-5) and then

randomized to a sham group or to a treatment group. The treatment group received injections of seven to 10 mL of ropivacaine, 0.5%, at the stellate ganglion under ultrasound guidance. A sham group received one to two ml of normal saline injected into the deep musculature adjacent to the anterior tubercle of C-6. The procedure was repeated two weeks later. At eight weeks the CAPS -5 was repeated. The primary outcome variable was the change from baseline to week eight in total symptom severity scores (TSSS).

Subjects were 113 adults with an average age of 37.3 years. The unadjusted mean change in TSSS was -12.2 points in the SGB group and -5.8 points in the sham group. In addition, compared to the sham group, those receiving SGB demonstrated better improvement on assessments of PTSD-associated symptoms, depression, distress, anxiety, pain symptoms, physical functioning, and mental functioning.

Conclusion: This study of military personnel with PTSD found that a stellate ganglion block, repeated after two weeks, could improve symptoms including depression, distress, anxiety, pain symptoms, physical functioning, and mental functioning.

Olmsted, K., et al. Effect of Stellate Ganglion Block Treatment on Posttraumatic Stress Disorder Symptoms: A Randomized Clinical Trial. *JAMA Psychiat.* 2020, February;77(2): 130-138.

CUMULATIVE INFLAMMATION AND CARDIOVASCULAR RISKS IN RHEUMATOID ARTHRITIS

Studies have shown that individuals with rheumatoid arthritis (RA) experience a higher rate of cardiovascular events. As systemic inflammation has been shown to be a risk factor for coronary artery disease, this study explored the relationship between cumulative inflammation and coronary plaque changes.

Subjects were 101 adult patients with RA who were enrolled in a coronary CT angiography study of subjects with subclinical coronary atherosclerosis. The participants were prospectively followed from baseline in 2010–2011 with measures of hypertension, diabetes, hyperlipidemia, tobacco use, waist height ratio, incident cardiac risk factors, disease activity, inflammation as measured by C-reactive protein (CRP) level, and coronary CT angiography. Plaque composition

was classified as noncalcified, mixed, or calcified. Coronary artery calcium (CAC) was quantified using the Agatston method. The cumulative inflammatory burden was calculated over time and compared to changes in coronary plaque.

Of the 101 patients included, total plaque increased in 40%. Progression of plaque was significantly related to older age, higher cumulative inflammation as measured by CRP and total prednisone dose. Those with plaque progression were older, more obese, hypertensive and had higher cumulative inflammation compared to those without progression ($p<0.05$). Longer exposures to biologics was associated with lower likelihood of plaque progression, lesion remodeling and constrained coronary artery calcium changes, independent of inflammation, prednisone dose or statin exposure (all $p<0.05$).

Conclusion: This prospective study of adult patients with rheumatoid arthritis found that increased cumulative inflammation and total prednisone dose were independent determinants of coronary artery plaque.

Karpouzas, G., et al. Impact of Cumulative Inflammation, Cardiac Risk Factors, and Medication Exposure on Coronary Atherosclerosis Progression in Rheumatoid Arthritis. *Arthritis Rheum.* 2020, March; 72 (3): 400–408.

PHYSICAL ACTIVITY LESS THAN THE RECOMMENDED DOSE AND BIOLOGIC RISK FACTORS

Current physical activity (PA) guidelines recommend that adults perform at least 150 minutes per week of moderate intensity PA or 75 minutes of PA at vigorous intensity. This study examined the dose-response relationship between PA and incidence of biological cardiovascular risk factors.

Data were obtained from the MJ Cohort Resource involving adults in Taiwan. This cohort has enrolled more than 600,000 participants since 1994. Participants completed a self-administered health and lifestyle questionnaire, underwent a physical exam and provided biologic samples. All were encouraged to return annually with data updated every year. For this study, adults were chosen with baseline information collected during the period of 1997 to 2016.

Participants were asked to report the intensity, frequency and duration of PA during the past weeks. A metabolic equivalent (MET; 3.5 mL/kg/min) value of 2.5 was designated as light PA, 4.5 as moderate PA, 6.5 as medium vigorous PA and 8.5 as high vigorous PA intensity. In addition all were assessed for cardiovascular risk factors, including obesity (\geq BMI 25 kg/m²), systolic blood pressure/diastolic blood pressure of >140 mmHg/90 mmHg, serum total cholesterol ≥ 240 mg/dL, triglycerides ≥ 150 mg/dL, high density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women. The level of PA was compared to the change in cardiovascular risk factors.

During a mean follow-up of six years, 13.5% developed obesity 11.3% hypertension 12.0% hypercholesterolemia, 8.3% atherogenic dyslipidemia, 15.2% metabolic syndrome and 4.3% type II diabetes. The PA was inversely associated with all of the risk factors (all $p>0.01$). Compared to the inactive, those with activity of at least 3.75–7.49 MET-h/week realized health benefits in obesity, hypertension, atherogenic dyslipidemia, metabolic syndrome and type II diabetes.

Conclusion: This study found that physical activity of less than half of the usually recommended amount improved the risk factors for cardiovascular disease.

Martinez-Gomez, D., et al. Physical Activity Less Than the Recommended Amount May Prevent the Onset of Major Biological Risk Factors for Cardiovascular Disease: A Cohort Study Of 198,919 Adults. *Br J Sport Med.* 2020 Feb;54(4):238-244.

DISABILITY AFTER MINOR STROKE AND TRANSIENT ISCHEMIC ATTACK

The Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) trial compared the effects of aspirin alone with dual antiplatelet therapy (DAPT) in preventing a recurrent vascular event, finding no significant difference. This post-hoc analysis examined the effect of treatment on overall disability.

At 90 days, of the 4,550 patients followed, disability occurred in 14.3% of the DAPT group and in 14.7% of the aspirin group ($p=0.69$). This disability was ascribed to the index stroke in 57%, recurrent stroke in

16% and another cause in 26%. However, there were fewer patients with disability due to the primary event in the DAPT arm than in the aspirin arm ($p=0.06$). The difference favoring DAPT was seen in patients enrolled with minor stroke as the index event (3.4% versus 5.2%; $p=0.02$).

Conclusion: This study of patients with a transient ischemic event or minor stroke found that disability related to the initial event was less likely among those treated with dual antiplatelet therapy, especially among those presenting with a minor stroke.

Cucchiara, B., et al. Disability after Minor Stroke and Transient Ischemic Attack in the POINT Trial. *Stroke*.2020, March;51(3):792-799.

MINOCYCLINE FOR ALZHEIMER DISEASE

Alzheimer disease affects 50 million people worldwide, with this expected to reach 135.5 million by the year 2050. This disease is associated with immune related and inflammatory genes. As minocycline is an anti-inflammatory tetracycline that crosses the blood brain barrier and inhibits the proinflammatory microglia, this study investigates the effect of this antibiotic for the treatment of patients with mild AD.

The Minocycline in Alzheimer Disease Efficacy (MADE) trial is a double-blind randomized clinical trial of individuals >50 years of age with mild AD. Participants were enrolled from May 23, 2014, to April 14, 2016. They were randomized to receive a placebo, minocycline at 200mg or minocycline at 400mg per day. Baseline data included the Standardized Mini-Mental State Examination (sMMSE) and a Bristol Activities of Daily Living Scale (BADLS) assessment. Outcome assessments were completed at baseline and months six, 12, 18, and 24. Data were analyzed for 403 subjects at 24 months, comparing the results of the minocycline groups combined to that of the placebo.

The mean duration of treatment was 11.4 months in the 400-mg group, 18.6 months in the 200-mg group, and 18.9 months in the placebo group. The sMMSE scores over 24 months were similar in the combined minocycline group and the placebo group (4.1 vs 4.3 points). The combined minocycline group had mean sMMSE scores 0.1 points

higher than the placebo group (95% CI, -1.1 to 1.2; $p=0.90$).

Conclusion: This study of patients with mild AD failed to demonstrate that minocycline could reduce the progression of the disease.

Howard, R., et al. Minocycline at 2 Different Dosages vs Placebo for Patients with Mild Alzheimer Disease. A Randomized Clinical Trial. *JAMA Neurol*. 2020; ;77(2):164-174.

BALL HEADING, MEMORY AND THE APOE ϵ 4 ALLELE

Prior studies have demonstrated an association between exposure to ball-heading in soccer and poor cognitive outcomes. Additionally, the apolipoprotein ϵ 4 (ApoE ϵ 4) allele has been associated with various neurodegenerative processes. This study assessed whether verbal memory is affected differently among those with the ApoE ϵ 4 allele after exposure to ball heading in soccer.

This prospective, observational study enrolled and genotyped 355 amateur soccer players, 18-55 years of age. At each study visit, players completed the Head-Count 12-Month Questionnaire, a metric used to estimate 12-month heading exposure. These results were used to stratify each players' ball heading exposure as low (first and second quartile), moderate (third quartile), or high (fourth quartile). Verbal memory was also assessed at each visit using the International Shopping List Delayed Recall task.

Using a linear regression, it was determined that higher levels of ball heading were associated with poorer performance on verbal memory ($p=0.001$). Among ApoE ϵ 4 positive players, there was a 4.1-fold greater deficit in verbal memory associated with high vs low heading exposure. In addition, there was an 8.5-fold greater deficit in verbal memory associated with high versus moderate heading exposure compared with ApoE ϵ 4 negative players.

Conclusion: This prospective study of amateur soccer players shows an association between ball heading exposure and poorer performance on verbal memory tasks, with a comparatively greater risk for those with the ApoE ϵ 4 allele.

Hunter, L., et al. Associations of Apolipoprotein E ϵ 4 Genotype and Ball Heading with Verbal Memory in Amateur Soccer Players. *JAMA*

Neurol. doi:10.1001/jamaneurol.2019.4828.

BLOOD-FLOW RESTRICTED VERSUS HEAVY-LOAD STRENGTH TRAINING

Lower limb muscle weakness is associated with reduced gait speed, increased risk of disability, and falls in the elderly. To improve muscle strength, the American College of Sports Medicine recommends regular heavy load resistance training (HLT) using resistance loads of 60-90% of the one repetition maximum. Blood flow restricted exercise using 20-30% of the one repetition maximum (LL-BFR) has also been used to improve maximal muscle strength. This literature review and meta-analysis compared the effect of LL-BFR to that of conventional HLT on maximal muscle strength among healthy individuals.

Literature was reviewed through September 23, 2019. Studies were included if focused on post intervention changes in maximal muscle strength. From this search were chosen 16 papers totaling 153 participants completing HLT, and 157 completing LL-BFR. The strength gains were compared between the groups.

No significant differences were noted between the two groups on the magnitude of gain in maximal muscle strength. In addition, the groups were similar in producing gains in muscle mass.

Conclusion: This meta-analysis comparing the efficacy of low load blood flow restriction resistance training and high load strength training found that improvements in strength and muscle mass were not statistically significant between the two.

Grønfeltdt, B., et al. Effect of Blood Flow Restricted Versus Heavy Load Strength Training on Muscle Strength: Systematic Review and Meta-Analysis. *Scand J Med Sci Sports* 2020 Feb 7. doi: 10.1111/sms.13632.

BLOOD PRESSURE THRESHOLDS DURING ENDOVASCULAR THERAPY

Endovascular therapy (EVT) has been shown to improve neurologic outcomes in patients with acute ischemic stroke. The optimal blood pressure target during EVT has not been defined. This study combined

three randomized clinical trials with comparable anesthetic and hemodynamic protocols to better understand the association between the specific blood pressure thresholds and neurologic outcomes after EVT. Data were obtained from the SIESTA, ANSTROKE and GOLIATH studies, all which randomized patients to general or local anesthesia, with blood pressure measured every five minutes during the EVT procedure. Neurologic outcomes were defined by the modified Rankin Scale (mRS) score after 90 days. The exposure variables include the systolic and mean arterial blood pressure (MABP) parameters and changes during the procedure.

For every 10 minutes of cumulated time with MABP of <70 mm Hg, there was a 30% increase in odds (adjusted OR, 1.30; $p=0.03$) of shifting toward worse outcomes on the mRS at 90 days. For every continuous 10 minutes with an MABP of <70 mm Hg, there was a 62% increase in odds ($p=0.005$) of shifting toward worse outcomes on the mRS at 90 days. For every 10 minutes of cumulated time with MABP greater than >90 mm Hg, there was an 8% increase in odds ($p<0.001$) of shifting toward worse outcomes on the mRS at 90 days.

Conclusion: This study of patients undergoing endovascular therapy for acute ischemic stroke, found that 90-day outcome scores were worse among those with an intra-procedural MABP of <70 mmHg for more than 10 minutes and MABP >90 mmHg for more than 45 minutes.

Rasmussen M., et al. Blood Pressure Thresholds and Neurologic Outcomes after Endovascular Therapy for Acute Ischemic Stroke: An Analysis of Individual Patient Data from 3 Randomized Clinical Trials. *JAMA Neurol.* doi:10.1001/jamaneurol.2019.4838.

ECCENTRIC BLOOD FLOW RESTRICTION EXERCISE AND THE CONTRALATERAL LIMB

Resistance training has been associated with increases in muscle strength and neuromuscular function in the contralateral, untrained limb. In addition, blood flow resistance (BFR) training has been shown to result in increases in muscle strength with lower weights than traditional exercise. Unlike concentric muscle

actions which rely, in part, on muscle spindles to modulate force production, eccentric muscle actions must inhibit the muscle spindle reflex to allow the muscle to lengthen under tension, a process requiring greater cortical activation. This study investigated whether cortical activation differs between those engaged in concentric (Con-BFR) and eccentric (Ecc- BFR) loading.

Subjects were 36 healthy adult women who were randomly assigned to receive four weeks of unilateral Ecc- BFR ($n = 12$), Con-BFR ($n = 12$) or control (no intervention, $n = 12$) group. Resistance training occurred three times per week and included 75, isokinetic muscle actions. At weeks zero, two and four, tests were made of eccentric peak torque, concentric torque and maximal voluntary isometric contraction torque. Tests of the untrained arm were made for eccentric peak torque, concentric peak torque, and maximal voluntary isometric contraction torque. Muscle thickness, and muscle activation were assessed at baseline, and up to week four.

After four weeks of training, increases in muscle strength of the untrained arm were 13% in the eccentric group and 11.2% in the concentric group ($p<0.05$). This gain of strength from baseline reached significance only in the eccentric group. There was no significant difference between the two groups in the change in muscle size or EMG amplitude.

Conclusion: This study found that eccentric but not concentric resistance training could significantly increase strength in the contralateral limb.

Hill, E., et al. Eccentric, But Not Concentric Blood Flow Restriction Resistance Training Increases Muscle Strength in The Untrained Limb. *Phys Ther Sport.* 2020, 43 (2020) 1-7.

VIBRATION VERSUS CRYOTHERAPY FOR ACHILLES TENDINOPATHY

Achilles tendinopathy (AT) is a common overuse injury characterized by pain, swelling, morning stiffness and impaired function during sports activity. In addition, some have suggested that the multifidus muscle has an important role in controlling the spinal segments, and plays an

important role in patients with lumbopelvic pain. This study assessed whether a load program with vibration or cryotherapy intervention could have influence in the morphology of the paraspinal muscles and lower limb function among individuals with AT.

This randomized study including adults with AT of at least three months duration. All subjects were engaged in an eccentric exercise program involving 90 repetitions twice a day for seven days per week. Those randomized to the vibration group (VG) performed the exercises while standing on a vibration platform with a frequency of 35 Hz and an amplitude of four mm for five minutes. Just prior to the exercise, those in the cryotherapy group (CG) immersed the affected lower limb in water cooled to $8\pm 2^\circ\text{C}$ for 17 min. All were assessed for disability related to Achilles tendon dysfunction using the Victorian Institute for Sport Assessment (VISA-A). The thickness of the multifidus muscle was recorded at the levels of the L4-5.

Multifidus thickness measures showed a significant ($p < 0.05$) decrease at 12-weeks in both groups with no significant differences between groups. Multifidus cross-sectional area (CSA) increased more in the vibration group than in the cryotherapy group ($p < 0.05$). Scores on the VISA-A were increased at four and 12-weeks in both groups, with no significant differences ($p > 0.05$) between them.

Conclusion: This study of patients with achilles tendinopathy failed to show a difference in outcome between those in an eccentric strengthening program plus cryotherapy and those treated with eccentric strengthening plus vibration.

Romero-Morales, C., et al. Vibration Increases Multifidus Cross-Sectional Area versus Cryotherapy Added to Chronic Non-Insertional Achilles Tendinopathy Eccentric Exercise. *Phys Therap Sport.* 2020, March; 42: 61–67.

EFFECT OF PRIOR COGNITIVE EXERTION ON PHYSICAL PERFORMANCE

Studies have shown carryover effects of cognitive tasks on subsequent physical performance. This study was design to summarize the findings of that literature.

This literature review and meta-analysis included studies of adults involved in cognitive exertion, followed by a physical task. Data were extracted from 79 articles with a total of 2,581 participants. From these data, physical performance was categorized into five groups including aerobic, dynamic resistance, isometric resistance, maximal anaerobic, and motor performance.

Overall, the meta-analysis revealed a small to medium negative effect size prior cognitive exertion on physical performance ($p < 0.001$). The largest significant negative effects were those of prior cognitive exertion on isometric resistance, motor and dynamic resistance performance. Following exposure to cognitive manipulations for under 30 minutes, the largest significant negative effects were observed for isometric resistance, dynamic resistance, and motor performance tasks, whereas a smaller significant negative effect was found for aerobic performance.

Conclusion: This literature review and meta-analysis found that central executive tasks requiring cognitive exertion, performed prior to physical performance resulted in a deterioration of that performance.

Brown, D., et al. Effects of Prior Cognitive Exertion on Physical Performance: A Systematic Review and Meta-analysis. *Sport Med.* 2020; 50(3):497–529.

EPTINEZUMAB FOR EPISODIC MIGRAINE

Migraine affects over one billion persons worldwide and is the second leading cause of disability. Calcitonin gene-related peptide (CGRP) plays a key role in mediation and initiating migraine. This study assessed the clinical effect of eptinezumab (ALD403), a humanized monoclonal antibody that selectively inhibits both a-CGRP and b-CGRP.

Subjects were adults 18-75 years of age with a diagnosis of migraines with 14 or less migraine days per month. Patients completed the eDiary to document all headaches, from the time of screening through week 48. Eligible patients were randomly assigned to receive eptinezumab 30 mg, 100 mg, 300 mg, or placebo in a 1:1:1:1 ratio. The total duration of the study was 60 weeks, with 12 scheduled visits. The primary efficacy endpoint was the change from

baseline in monthly migraine days (MMDs) over weeks 1–12, assessed using eDiary data.

Data were available for 888 patients who received treatment and were included in the efficacy population. Of these 21.7% discontinued prior to completion of the study. The mean monthly headaches were reduced from baseline by four in the 30mg group ($p = 0.0046$, not significant per protocol), 3.9 in the 100 mg group ($p = 0.00182$) and 4.4 in the 300 mg group ($p = 0.0001$). The preventative effects were evident within the first days after administration. During the first month following administration, nearly a third of patients treated with eptinezumab 100 mg (30.8%) and 300 mg (31.5%) experienced a 75% or greater reduction in migraine days

Ashina, M., et al. Eptinezumab In Episodic Migraine: A Randomized, Double Blind Placebo Controlled Study (PROMISE I). *Cephalalgia.* 2020, March; 40(3):241-254.

EARLY MOBILIZATION AFTER INTRACEREBRAL HEMORRHAGE

Data have demonstrated that mobilization within 72 hours of intensive care unit (ICU) admission is beneficial, while mobilization for training earlier than 24 hours may be counterproductive. This study investigated the effect of out of bed mobilization among patients with acute intracerebral hemorrhage (ICH).

This prospective, blinded, randomized controlled trial included patients with an ICH, admitted to a stroke center in Taipei, Taiwan. The subjects were patients with hemiparesis and with no contraindications to mobilization. Those with secondary ICH due to trauma, surgery, hemorrhagic transformation from stroke or an underlying mass were excluded. All were assessed using the Functional Independence Measure (FIM) for up to three months after stroke. The primary endpoint was the total score on the motor subscale of the FIM. Those randomized to the early mobilization (EM) group were engaged at 24 to 72 hours with out of bed mobilization for 30 minutes five days a week. Those in the control group underwent out of bed mobilization after ICU discharge. Outcome measures were collected at

baseline, and then at two, four and 12 weeks after stroke onset.

Subjects were 60 patients admitted to the ICU within 24 hours. The EM group demonstrated significant improvements in FIM-motor scores at two and four weeks after stroke. At 12 weeks the EM group was superior to the control group ($p = 0.004$). The mean duration of stay in the stroke center was significantly less in the EM group (86.22 days) compared to the control (119.2 days; $p = 0.004$).

Conclusion: This study of patients with acute hemorrhagic stroke found that those undergoing mobilization within 24 to 72 hours of stroke onset had a shorter length of stay in the ICU, as well as better motor function scores at three months, compared to those receiving standard care.

Yen, H., et al. Early Mobilization of Mild-Moderate Intracerebral Hemorrhage Patients in a Stroke Center: A Randomized Controlled Trial. *Neurorehabil Neural Repair.* 2020; 34 (1): 72–81.

CATHEPSIN K INHIBITION FOR OSTEOARTHRITIS

Cathepsin K is a cysteine protease involved in bone resorption and cartilage degradation. Early trials of a reversible inhibitor of Cathepsin K, MIV-711, have shown a significant reduction in biomarkers of bone resorption and cartilage loss. This study assessed the effect of MIV-711 on the symptoms of osteoarthritis (OA).

Eligible subjects were 40 to 80 years of age with a diagnosis of primary OA of the knee, and with an average knee pain score of at least four on a ten-point visual analogue pain scale. The participants were randomized to receive MIV-711 100mg, MIV-711 200mg or placebo once daily for 26 weeks. The primary outcome variable was change from baseline to week 26 and average pain severity over the previous week. The key secondary outcome measure was the change from baseline to week 26 in the medial femoral bone area in the target knee joint on MRI.

The average pain severity in the target knee decreased from baseline to week 26 by a mean of 1.4 in the placebo group, 1.7 in the 100 mg group and 1.5 in the 200 mg group. None of the comparisons reached

(Continued from page 2)

*Vanessa L. Wanjeri, M.D.
Matthew Amodeo, M.D.
Univ. of Pennsylvania, Phila, PA

*Andrew Minkley, M.D.
University of Washington, Seattle, WA

*Bonnie Weigert, M.D.
Hazel Mathes, D.O.
Univ. of Wisconsin, Madison, WI

*Aileen Giordano, M.D.
Univ. Of VA, Charlottesville, VA

*Adem Akatas, D.O.
*Michael Krill, M.D.
Margaret Beckwith, M.D.
Alexandra Fogarty, M.D.
Seth M. Katzen, D.O.
Washington Univ., St. Louis, MO

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

Subscription Manager
Michael P. Burke, M.S.

***Regional Managing Editors have attested that they have no financial conflict of interest when choosing articles that appear in Rehab in Review.**

the mean change (deterioration) from baseline bone area was 23.3 mm² in the placebo, 7.9 mm² in the 100 mg group and 8.6 mm² in the 200 mg group. An attenuation of thinning of the medial femoral joint cartilage was observed in both treatment groups as compared with the placebo. Significance was reached for the 100 mg but not the 200 mg group. At week 26, significantly better changes in bone biomarkers including serum CTX-I and urine CTX-II levels were observed in the treatment groups as compared with the placebo group (p<0.001). Adverse events were reported in similar numbers in all groups.

Conclusion: This study of patients with osteoarthritis of the knee found that an inhibitor of Cathepsin K could significantly reduce bone and cartilage deterioration, though no improvement in pain was achieved.

Conaghan, P., et al. Disease Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis: A Randomized Controlled Trial. *Ann Intern Med.* 2020, January 21; 172: 86–95.

Rehab in Review (RIR) is produced monthly by physicians in the field of Physical Medicine and Rehabilitation (PM&R), with the cooperation and assistance of Emory University School of Medicine, Department of Rehabilitation Medicine. The summaries appearing in this publication are intended as an aid in reviewing the broad base of literature relevant to this field. These summaries are not intended for use as the sole basis for clinical treatment, or as a substitute for the reading of the original research.

The Emory University School of Medicine designates this journal based activity for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. The Emory University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The journals are offered as a CME accredited activity for 3 years from the date of original publication.

RIR is affiliated with the Association of Academic Physiatrists, the World Health Organization, and the Chinese and Indian Societies of PM&R and endorsed by the International Society of Physical and Rehabilitation Medicine.

Private subscriptions are available by email at rehabinreview@aol.com or by fax or phone at (417) 779-9101.

ISSN # 1081-1303



REHAB IN REVIEW

Produced by the Department of
Rehabilitation Medicine, Emory
University School of Medicine



EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of
Rehabilitation
Medicine

Expanding the frontier of rehabilitation sciences in research, teaching, and patient care