

BONES & BRAIN

IN REVIEW

TM

Volume 32 Number 2

Published by Physicians
In Physical and neurological Medicine

February 5, 2024

HELICOBACTER PYLORI INFECTION AND INCIDENT RISK OF DEMENTIA

Alzheimer's disease (AD) is one of the leading causes of disability in the world. A growing body of evidence focuses on infectious disease as a contributing factor to AD, with *Helicobacter pylori* (*H pylori*) among these. This study explored the association between *H pylori* infection and the incidence of dementia.

The subjects were participants in a French, epidemiologic, prospective study on aging, initiated in 2007. Retired farmers, 65 years of age or older at baseline, living in southern France, were randomly recruited from the Farmers Health Insurance System. Every two to three years, data were collected on sociodemographic, environmental, neuropsychological, functional, and medical status. Blood samples were taken for serologic detection of *H pylori* infection. The primary outcome measure was a comprehensive neuropsychological assessment, including global cognitive abilities, episodic memory, abstract thinking, and verbal fluency. The neuropsychological data were compared by *H pylori* status.

Data were analyzed for 689 participants with a mean age of 75.8 years. Of these, 29% had a positive *H pylori* serology (HP+). Compared to those with negative serology (HP-), the HP+ group had a greater risk of incident dementia over seven years ($p=0.030$), as well as AD ($p<0.001$). In the adjusted analysis, *H pylori* remained independently associated with AD ($p<0.001$).

Conclusion: This prospective study of community dwelling adults, 65 years of age or older at baseline, found that infection with *H pylori* at baseline was associated with an increased risk of dementia.

Hernandez-ruiz, V., et al. Association between Helicobacter Pylori Infection, and Incident Risk of Dementia: The AMI Cohort. *J Am Geriatr Soc.* 2024, Jan 23. doi: 10.1111/jgs.18748.

LEISURE TIME PHYSICAL ACTIVITY AND CARDIOVASCULAR MORTALITY

Cardiovascular disease (CVD) is the foremost cause of death in the United States. Recently, the Centers for Disease Control and Prevention reported that over 25% of U.S. adults do not engage in leisure time physical activity (LTPA) outside of their work. This study assessed the relationship between a lack of LTPA and cardiovascular mortality.

Data were obtained from a nationwide, U.S., county-level data bank spanning from 2011 to 2019. The primary variable of interest was the county level age-adjusted proportion of adults who reported no engagement in LPTA outside of work (no-LTPA). Annual age-adjusted cardiovascular mortality (AACVM) was calculated per county, with specific cardiovascular disease mortality identified using ICD 10 codes.

Data were obtained from 2,900 US counties, including 309,886,995 individuals. Among those studied, 7,381,448 (2.4%) CV deaths were recorded between 2011 and 2019, with a mean of 219.9 AACVM deaths/100,000 persons. Between 2011 and 2019, overall AACVM decreased significantly across the three tertiles of no-LTPA rates. In the fully adjusted model, no-LTPA rates were associated with an increased risk of AACVM ($p<0.001$). Not engaging in LTPA was associated with a relatively greater risk of AACVM among middle-aged adults as compared to the elderly ($p<0.001$), among Hispanics ($p<0.001$) and Blacks ($p<0.002$), than among Whites, and among the elderly, with the highest risk among elderly blacks.

Conclusion: This study found that counties with high rates of adults not engaging in leisure time physical activity experience elevated cardiovascular mortality rates, most striking among middle-aged women and elderly blacks.

Abohashem, S., et al. Lack of Leisure Time Physical Activity and Variations in Cardiovascular Mortality across U.S. Communities: A Comprehensive, County-Level Analysis (2011-2019). *Br J Sports Med.* 2024 Jan 10:bjssports-2023-107220.

VAGUS NERVE STIMULATION FOR NARCOLEPSY

Vagus nerve stimulation (VNS), used for the treatment of patients with epilepsy, has been shown to have side effects, including increased alertness and reduced sleepiness. As narcolepsy is characterized by abnormal regulation of the sleep-wake cycle, this study assessed the efficacy of VNS as a treatment for narcolepsy.

Patients were 18 years of age or older, diagnosed with narcolepsy. All had received VNS for the treatment of epilepsy or major depressive disorder. Patients without narcolepsy who had had been treated with VNS for depression or epilepsy served as controls. To measure sleepiness, the Epstein Sleepiness Scale (ESS) was used, beginning one week prior to the onset of VNS and at three and six months after the implantation. All subjects were assessed for depression using the Beck Depression Inventory-2 (BDI-2).

Data were collected for 18 patients with narcolepsy and 18 controls. Compared to baseline values, the mean ESS scores in the narcolepsy group had improved significantly at three ($p<0.05$) and six ($p<0.01$) months. No significant improvement was noted in the control group. Multiple regression analysis revealed that the effect of VNS on ESS was independent from improvement in depression as measured by the BDI-2.

Conclusion: This study of patients with narcolepsy, found that vagus nerve stimulation resulted in an improvement in daytime sleepiness as measured by the Epstein Sleepiness Scale.

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

Assistant Editor

Roberta Bell, Ph.D.

Assistant Executive Editors

Tracie E. McCargo, Ph.D. Harvard University, Cambridge, MA
Jose Villalon-Gomez, MD Emory University, Atlanta, GA

Contributing Editors

*Alvin Chang, M.D. Casa Colina, Azusa, CA

*Michael Stephanides, M.D. Gavin Ajami, M.D. Dorothy Cabantan, MD Andy Doan, M.D. Derek Fox, M.D. Nicholas Hooper, M.D. Anuj Marathe, M.D. Yash Mehta, M.D. Emory Univ. SOM, Atlanta, GA

*Arieen Loo-Hernandez, D.O. *Zachary Poché, M.D. Michael Connors, M.D. Chance Melancon, MS4 Jacob Meariman, MS4 LSU Health, New Orleans, LA

*Jack Leal, D.O. Peter Atallah, D.O. Elliott Berry, M.D. Jenzel Espares, D.O. Karthik Kamath, D.O. Leslie Wong, D.O. Nassau Univ., East Meadow, NY

*Jessica Marone, M.D. *Olumide Sokunbi, M.D. Shivam Patel, D.O. Sean Weber, D.O. NW Univ. Feinberg SOM, Chicago, IL

*Ray Pak, M.D. Michelle Cho, M.D. Nate Michalak, M.D. NYMC/NYCH+H, New York, NY

*Sohyun Kang, M.D. Lorna Collins, M.D. Madhavan Elangovan, M.D. Jack Haberl, M.D. NY-Presbyterian, New York, NY

*Max Lee, M.D. *Navjot Singh, D.O. Brandon Burg, D.O. Dorothy Cabantan, MS4 David Jevotovsky, M.D. Chun Maung, D.O. Zaineb Zubair, MS4 NYU, New York, NY

*Pirapon Leo Chaidarun, M.D. *Saarang Singh, M.D. Josh Ballway, M.S. Amog Mysore, M.S. Shivam Rangolia, M.D. Rutgers, NJMS, Newark, NJ

*Anam Purewal-Kossack, M.D. Maria Lee, M.D. SUNY Downstate, Brooklyn, NY

*Preethika Venugopal, D.O. Edward Chang, D.O.

Winter, Y., et al. Vagus Nerve Stimulation for the Treatment of Narcolepsy. **Brain Stimul.** 2024, Jan 4;17(1):83-88.

SHOCKWAVE THERAPY FOR ATHLETES

A growing body of evidence suggests that extracorporeal shockwave therapy (ESWT) may be effective for the management of sports related injuries. This systematic review was designed to better understand the efficacy of ESWT for the outcomes of sport-related injuries.

A literature review was completed for studies evaluating the efficacy of ESWT for athletes, physically active individuals, and occupational groups requiring regular physical activity, such as military cadets. From this review, 609 studies were initially identified, from which 56 were chosen, involving 1,874 athletes or physically active individuals. Included among these were 19 randomized, controlled trials. The Oxford Level of Evidence rating was used to evaluate each study, with 10 level I, three level II, 10 level III, 13 level IV, and 12 level V studies identified.

Focusing on data from the level-one studies, ESWT was found to be an effective treatment for plantar fasciitis, lateral epicondylitis, and proximal hamstring tendinopathy. ESWT was an effective adjunct to exercise treatment for patients with medial tibial stress syndrome and osteitis pubis.

Conclusion: This literature review of studies of extracorporeal shockwave therapy as a treatment for athletes or active individuals found strong evidence that this modality is effective for treating plantar fasciitis, lateral epicondylitis, and proximal hamstring tendinopathy.

Rhim, H., et al. Use of Extracorporeal Shockwave Therapies for Athletes and Physically Active Individuals: A Systematic Review. **Br J Sport Med.** 2024, Jan 16. doi: 10.1136/bjsports-2023-207567.

POTASSIUM RICH VEGETARIAN DIET FOR PAIN IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a lifelong autoimmune disease characterized by painful polyarthritis and articular deformities. This study investigated the use of oral potassium

in a vegetarian diet as a supplement for the treatment of RA.

Subjects were 155 symptomatic adult patients recruited from a community rheumatoid center. The patients were randomized to one of three arms, a potassium rich, vegetarian diet (PVD) containing $\geq 3,500\text{mg/day}$ of elemental potassium, PVD plus a potassium enriched (2,638 mg) food supplement (PVD+KFS) to increase daily potassium to 5.5 g/day, and a vegetarian diet, as per Indian recommendations, which served as a control diet (CD). The primary efficacy point was improvement in the Visual Analog Scale for Pain (VAS-P) from baseline to week 16.

From baseline to week 16, the VAS-P was significantly more improved in the PVD+KFS group than in the PVD ($p=0.04$) and CD ($p=0.02$) groups. Univariate analysis revealed that a daily potassium intake of 5 g or more was significantly associated with a VAS of four or less (Odds Ratio (OR) 3.14). Regression analysis revealed that significant predictors of low pain ($\text{VAS} \leq 4$) were a daily potassium intake of $\geq 5\text{g}$ (OR 2.87) and methotrexate use (OR 16.1).

Conclusion: This study of patients with symptomatic rheumatoid arthritis found that a vegetarian diet and food supplementation with high oral potassium intake could significantly reduce painful symptoms.

Kianifard, T., et al. Adjunct Role of Potassium-Rich Vegetarian Diet and a Novel Potassium Food Supplement to Improve Pain in Chronic Rheumatoid Arthritis on Supervised, Standard Care: A Randomized, Controlled Study. **BMJ Nutr Prev Health.** 2024. doi: 10.1136/bmjnp-2023-000674.

LONG-TERM PSYCHOLOGICAL OUTCOMES FOLLOWING STROKE

Research concerning the emotional consequences of stroke has predominantly focused on depression. This study was designed to provide a more complete understanding of the prevalence and nature of long-term psychological outcomes following stroke.

The OX-CHRONIC study recruited subjects from acute stroke wards within the John Radcliffe Hospital in the United Kingdom between 2012 and 2020. Those who were two or more years post-stroke underwent a battery of

neuropsychological tests addressing a range of possible cognitive impairments. Caregivers were also administered measures, including the Caregiver Strain Index, the Informant-GDS, and the Informant Questionnaire for Cognitive Decline in the Elderly (IQ-CODE).

Data were completed for 105 patients with a stroke (wave one), with 90 completing reassessment one year later (wave two). At wave one, 65.3% were classified as having a domain-general cognitive impairment (earning a Montreal Cognitive Assessment (MoCA) score of below 26). A stroke specific, multidomain, cognitive impairment (a MoCA score of below 22) occurred in 30.6% at wave one and in 34.1% at wave two.

On the Oxford Cognitive Screen, 45.9% were found to have at least one cognitive impairment. Attention (27.1%) and executive function (40%) were the most frequently impaired abilities. Elevated depression and anxiety scores were found in 23.5% and 22.5% of the subjects, respectively. Fatigue (51.4%) and apathy (40.5%) rates remained high at wave two.

Conclusion: This study of patients, all at least two years post-stroke, found that over half experienced psychological difficulties, including cognition, mood, and fatigue issues, which impacted long-term quality-of-life.

Kusec, A., et al. Long-Term Psychological Outcomes following Stroke: the OX-CHRONIC Study. *BMC Neurol.* 23, 426 (2023). <https://doi.org/10.1186/s12883-023-03463-5>.

EXERGAME, COGNITIVE TRAINING, AND FALLS IN THE ELDERLY

Falls in the elderly are the second leading cause of unintended injury deaths worldwide. Robust evidence exists that exercise and, in particular, balance training can prevent falls in older people. This study tested the smart±step in-home computerized gaming system, with eight games that can be played either using a touchpad while seated (cognitive training) or by stepping on target panels on a step mat (exergame training).

The subjects were 769 elderly, community dwelling individuals, randomized to one of three groups, cognitive training (CT), exergame step training on a computerized mat (E-ST), or a control group (CON)

given an education booklet on healthy aging and fall prevention. The CT and E-ST groups received an initial orientation (60 to 120-minutes duration) and follow-up home visit (30 to 60-minutes duration). The primary outcome variable was the number of falls reported in the 12 months after onset of the program, as compared with baseline.

Over 12 months, the groups trained for a mean of 79.7 minutes per week. During the 12-months' follow-up period, the proportion of people who reported one or more falls were 36.0% for the E-ST group, 42% for the CT group, and 48.2% for the CON group. Falls with injury were reported by 25% of the E-ST group, 29.8% of the CT group, and 31% of the CON group. No serious intervention-related adverse events were reported during the trial.

Conclusion: This study of elderly individuals living in the community found that a home based exergame training program could reduce falls by 26% over 12 months.

Sturnieks, D., et al. Exergame and Cognitive Training for Preventing Falls in Community-Dwelling Older People: A Randomized, Controlled Trial. *Nature Med.* 2024, Jan; 30(1): 98-105.

ENHANCED COGNITIVE PERFORMANCE REDUCES FRACTURE RISK

Bone fractures in older adults are a global public health issue. As recent observational studies have suggested a potential link between cognitive performance and fracture risk, this study explored the causal effects of cognitive performance on the probability of site-specific fractures.

The authors identified single-nucleotide polymorphisms (SNPs) pertinent to cognitive performance from the UK Biobank and Cognitive Genomics Consortium (COGENT) dataset. Fracture cases were identified from the FinnGen Consortium and UK Biobank, which included 3,983 cases of femur fracture, 2,859 cases of lumbar pelvic fracture, 5,824 cases of upper arm-shoulder fracture, 4,070 cases of rib-sternum-thoracic vertebral fracture and 4,693 cases of ankle fracture. Using these data Mendelian Randomization methods were used to determine the influence of cognitive performance on fracture incidence.

The MR analysis found a potential causal effect of cognitive performance on the risk of lumbar

spine-pelvis fracture ($p=0.023$). An MR analysis found a potential causal effect of better cognitive performance and lower risk of ribs-sternum-thoracic spine fracture ($p=0.029$). No causal performance was found between cognitive performance and wrist, upper arm-shoulder, femur, leg, or ankle fractures.

Conclusion: This study uses Mendelian randomization to describe a causal relationship between enhanced cognitive performance and a decreased risk of fractures at the ribs, sternum, and thoracic spine.

Luo, S., et al. Does Enhanced Cognitive Performance Reduce Fracture Risk? A Mendelian Randomization Study. *Aging.* 2023 Dec 31;15(24):14985-14995.

ARTHROGENIC MUSCLE INHIBITION AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

Arthrogenic muscle inhibition (AMI) is a frequent but underrecognized cause of quadriceps activation failure and knee extension deficit after knee injury. While this is thought to be a protective mechanism against further injury, it can also pose a challenge for effective recovery. This study was designed to determine the incidence and factors associated with AMI after an anterior cruciate injury (ACL) injury.

Subjects were consecutive patients with an ACL injury. All underwent physical exams and completed patient reported outcome measures, including a visual analog scale (VAS) of pain, subjective International Knee Documentation Committee (IKDC) scores, Lysholm scores, Knee Injury and Osteoarthritis Outcome Scores (KOOS), Simple Knee Values, and pre-entry activity levels. The Sonnert-Cottet classification was used to grade AMI. The primary outcome variable was the reversibility of grades 1A and 2A AMI.

Of the 300 patients enrolled in this study, 170 demonstrated AMI. Those with AMI obtained significantly worse scores on the Lysholm, IKDC, Simple Knee Value, and KOOS than patients without AMI ($p < 0.0001$). Of those with AMI, 79% showed a resolution of their AMI after simple exercises involving hamstring fatiguing and reactivation of quadriceps muscle contraction.

Conclusion: This study of patients with acute anterior cruciate ligament injuries found that more than

half exhibited features of arthrogenic muscle inhibition.

Sonnery-Cottet, B., et al. Incidence of and Risk Factors for Arthrogenic Muscle Inhibition in Acute Anterior Cruciate Ligament Injuries: A Cross-Sectional Study and Analysis of Associated Factors from the SANTI Study Group. *Am J Sports Med.* 2024, January; 52(1): 60-68.

APIXABAN FOR STROKE PREVENTION IN SUBCLINICAL ATRIAL FIBRILLATION

Studies have shown that short episodes of atrial fibrillation (AF) are common, even among patients with no other evidence of clinical AF. This study compared the efficacy of aspirin with that of apixaban for reducing the risk of stroke among adults with asymptomatic AF.

The Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Subclinical Atrial Fibrillation (ARTESIA) trial included patients, 55 to 75 years of age, with subclinical AF detected and a CHA₂DS₂-VASc score of three or higher. The subjects were randomized to receive either apixaban, 5 mg twice daily (reduced to 2.5 twice daily as indicated by product labeling), or aspirin, 81 mg daily. The primary efficacy outcome variable was a composite of stroke and systemic embolism.

During the study, 4,012 patients underwent randomization, 2,015 to the apixaban group and 1,997 to the aspirin group. During follow-up, stroke or systemic embolism occurred in 55 patients of the apixaban group (0.78% per patient-year) and 86 patients of the aspirin group (1.24% per patient-year; $p=0.007$). Of those who experienced a stroke, a fatal or disabling stroke (score on the Modified Rankin Scale, 3 to 6) occurred in 33% of the apixaban group and 43% of the aspirin group. The risks of major bleeding were 1.71% per patient-year with apixaban and 0.94% per patient-year with aspirin ($p=0.001$).

Conclusion: This study, the ARTESIA trial of patients with subclinical atrial fibrillation and risk factors for stroke, found that the risk of stroke or systemic embolism was lower by 37% among those prescribed apixaban than with aspirin, and that the risk of disabling or fatal stroke was lower by 49%.

Healy, J., et al. Apixaban for Stroke Prevention in Subclinical Atrial

Fibrillation. *N Eng J Med.* 2024, January 11; 390: 107-117.

AGATROBAN FOR ISCHEMIC STROKE WITH EARLY NEUROLOGIC DETERIORATION

Early neurologic deterioration (END) after an acute ischemic stroke (AIS) is relatively common and is associated with an increased risk of intracranial hemorrhage. Therefore, guidelines recommend against urgent anticoagulation with AIS. As argatroban is a rapid but short acting direct thrombin inhibitor, this study evaluated the efficacy of argatroban for END in AIS

Subjects were 628 adults with an AIS and experiencing END. Both the control and treatment groups received standard therapy, including oral mono or dual antiplatelet therapy such as aspirin and/or clopidogrel, according to Chinese Stroke Association guidelines. Those randomized to the treatment group also received argatroban 60mg/day for two days, followed by 20 mg/day for seven days. The primary endpoint was a good functional outcome at 90 days (modified Rankin Scale (mRS) score of zero to two).

The primary outcome measure was realized at 90 days in 80.5% of the treatment group and 73.3% of the control group ($p=0.04$). This difference remained in the adjusted analysis ($p=0.03$). The occurrence of symptomatic intracranial hemorrhage was 0.9% in the argatroban and 0.7% of the control group ($p=0.78$).

Conclusion: This study of patients with acute ischemic stroke followed by early neurologic deterioration found that adding seven days of argatroban to traditional antiplatelet therapy resulted in a greater likelihood of a good functional outcome at 90 days.

Zhang, X., et al. Argatroban in Patients with Acute Ischemic Stroke with Early Neurological Deterioration. *JAMA Neurol.* 2024. doi: 10.1001/jamaneurol.2023.5093.

OUTCOMES OF YOUNGER PATIENTS UNDERGOING TOTAL ANKLE ARTHROPLASTY

Post-traumatic arthritis is a common diagnosis for those who undergo total ankle arthroplasty (TAA). This study assessed the effect of age on the outcomes of these procedures.

This retrospective study included data collected from primary TAA surgeries performed between March of 2000 and October of 2020 at a single institution. Data were obtained from the records of 1,115 patients, 22 to 89 years of age. These subjects were placed into groups by age, including those 55 years of age or younger, those 55 to 70 years of age, and those over 70 years of age. Follow-up occurred at a mean of 5.6 years. Outcomes were measured with the Foot and Ankle Disability Index (FADI), the Short Musculoskeletal Function Assessment (SMFA), and the Foot and Ankle Outcome Score (FAOS).

Repeat surgery occurred in 19.9% of the 55-year-old or younger group, 11.7% of the 55- to 70-year-old group, and 6.5% of the over 65-year-old group ($p<0.001$). The 55-year-old or younger group also had the greatest risk of implant failure ($p=0.019$) and the worst numerical pain score at final follow-up ($p<0.001$). Across all subscales of the FAOS measure, except for the activities of daily living subscale, those 55 years of age or younger earned the worst, mean post-operative scores at one year and at final follow-up ($p\leq0.001$) and demonstrated smaller improvements on measures of activities of daily living ($p<0.006$).

Conclusion: This large, retrospective study of patients undergoing total ankle arthroplasty found that, compared with older patients, those under 55 years of age at the time of surgery had the highest rates of complications, implant failures, and component removals.

Anastasio, A., et al. Younger Patients Undergoing Total Ankle Arthroplasty Experience Higher Complication Rates and Worse Functional Outcomes. *J Bone Joint Surg.* 2024, January 3: 106-A(1): 10-20.

PANAX NOTOGINSENG FOR COPD WITH BLOOD HYPERCOAGULABILITY

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality throughout the world. If not properly treated, this disorder can lead to hypoxia and carbon dioxide storage. Chronic hypoxia can then lead to a hypercoagulable state (HCS), which can further aggravate COPD. As studies have shown that Panax notoginseng saponins (PNS), the active component of Panax

notoginseng, may improve blood hypercoagulability, circulation, and lung function, this meta-analysis was designed to better understand the efficacy of PNS for COPD.

A literature review was conducted for studies involving "Panax notoginseng saponins", "xuesaitong", "xuesetong", "xueshaotong", "lulutong", "sanqishutong", "chronic obstructive pulmonary disease", "hypercoagulable state of blood", "hypercoagulable blood", and "pre-thrombosis state". Primary outcome variables included forced expiratory volume in one second percent of predicted (FEV1%), fibrinogen (FIB), and partial pressure of oxygen (PaO₂). Secondary outcomes included total clinical efficiency, FEV1/FVC, D-dimer (D-D), activated partial thromboplastin time (APTT), prothrombin time (PT), whole blood viscosity at high cut (BVH), whole blood viscosity at low cut (BVL), plasma viscosity (PV), and decreased carbon dioxide pressure (PaCO₂).

The literature search located 20 randomized, controlled studies involving 1,831 patients, including 926 in experimental groups and 905 in control groups. The meta-analyses found that treatment with PNS improved total clinical efficacy (p<0.0001), FEV1% (p=0.001), FEV1/FVC (p=0.0418), FIB (p=0.004), D-D (p<0.0001), BVH (p<0.0001), BVL,9 (p< 0.0001), and PVD (p=0.0080). Blood gas data demonstrated improvement with PNS as compared to the control condition in PaO₂ (p< 0.0001) and PaCO₂ (p<0.0001).

Conclusion: This literature review and meta-analysis of studies of patients with COPD found that Panax notoginseng saponins significantly improved overall clinical efficiency, pulmonary function, hypoxia, hemodynamics, and blood hypercoagulability and reduced blood viscosity.

Zhou, R., et al. Clinical Efficacy and Safety of Panax Notoginseng Saponins in Treating Chronic Obstructive Pulmonary Disease with Blood Hypercoagulability: A Meta-Analysis of Randomized, Controlled Trials. **Phytomed.** 2024, March; 125: 155244.

DISCOGEL FOR DEGENERATIVE DISC DISEASE

As a new treatment for back pain, ethanol gel chemonucleolysis (EGCh) uses DiscoGel, a class III medical device that consists of ethanol gelled with cellulose and a suspension of

tungsten, injected into the intervertebral. DiscoGel is thought to work by drying out the nucleus pulposus within the disc, reducing intradiscal pressure, thereby relieving mechanical compression on the nerve roots. This study used high intensity zones (HIZ) observed on T2 MRI sequences to assess the efficacy of EGCh on the radiologic picture of the intervertebral disc.

A group of 45 patients with DDD were scheduled for EGCh using DiscoGel. Assessments included MRI and the Core Outcome Measures Index (COMI), administered at baseline and up to 12 months after the procedure. Pain was assessed using visual analogue scales (VAS).

The MRI demonstrated HIZs at 52 levels in 34 patients with the dominant symptom of axial pain. After the surgery, there was an increase in disc height at the treated level in 61% of patients, a reduction in disc protrusion in 35 cases, and a reduction in the HIZs in 28 cases. The baseline COMI scores were 6.76 in the HIZ+ group and 6.48 in the HIZ- group. After surgery these improved by 2.70 in the HIZ+ and 1.76 in the HIZ- group (p=0.03). Mean VAS pain scores improved from 6.67 at baseline to 2.37 at follow-up in the HIZ+ group and from 6.31 to 3.09 in the HIZ- group.

Conclusion: This study of patients with discogenic back pain found that the presence of high-intensity zones on baseline T2 MRI scans may serve as a prognostic indicator of the effectiveness of ethanol gel chemonucleolysis using DiscoGel.

Latka, K., et al. Effect of DiscoGel Treatment of the Intervertebral Disc at MRI. **Clin Radiol.** 2023, December; 78(12): 928-934.

AEROBIC EXERCISE AND SKELETAL MUSCLE MASS

Studies have shown a strong association between skeletal muscle mass (SMM) and numerous health outcomes. This study was designed to understand whether aerobic exercise contributes to the preservation or increase in total or regional skeletal muscle mass (SMM).

This secondary analysis was completed using data from four randomized trials, including 238 sedentary adults with a body mass index >30kg/m². The treatment group was assigned exercise ranging from 50 -75% of VO₂ peak five days per

week, with controls asked to maintain their normal lifestyles. Skeletal mass was determined using MRI, with adipose and SMM converted to mass units. Baseline and follow-up values for VO₂ peak, weight, waist circumference, and adipose tissue were recorded.

Compared with baseline, all MRI-measured adipose tissue depots were reduced, and cardiorespiratory fitness increased more in the aerobic exercise group than in the control group (p<0.001). Aerobic exercise was associated with a small reduction in whole body SMM and upper body SMM, as compared to those of controls. The skeletal muscle mass adipose tissue ratio increased after aerobic exercise (p<0.001).

Conclusion: This analysis of four pooled, randomized, controlled trials involving sedentary adults found that aerobic exercise does not increase skeletal muscle mass.

Ross, R., et al. Does Aerobic Exercise Increase Skeletal Muscle Mass in Female and Male Adults? **Med Sci Sports Exerc.** 2024, Jan 8. doi: 10.1249/MSS.0000000000003375.

NEUROMUSCULAR ELECTRICAL STIMULATION FOR HOSPITALIZED PATIENTS

Hospitalized patients frequently develop hospital acquired disability. While early rehabilitation improves outcomes, in practice, many patients are too medically unstable or excessively symptomatic for participation. Neuromuscular electrical stimulation (NMES) uses a low frequency current, transmitted through electrodes to induce involuntary muscle contraction. This literature review and meta-analysis was designed to better understand the efficacy of NMES for the treatment of hospitalized adults.

The literature review identified studies of adult patients with NMES applied to a limb, with outcomes including muscle strength, sarcopenia, function, hospital length of stay, and adverse events. From this review, 38 studies were chosen for inclusion in the qualitative analysis and 39 papers were included in the meta-analysis, for a total of 1,452 patients.

The meta-analysis showed a small treatment effect of NMES as compared to the control condition (p<0.00001). Muscle size was improved in the NMES group compared to controls (p<0.005),

evident in both ICU and non-ICU patients ($p < 0.005$ for both). Walking performance was significantly improved in the NMES group ($p < 0.0001$), with the effect most pronounced in non-ICU patients. No significant difference was found between the conditions in hospital length of stay.

Conclusion: This study of hospitalized patients found that neuromuscular electrical stimulation resulted in improved muscle strength, muscle size, walking performance, and functional mobility.

Alqurashi, H., et al. The Effects of Neuromuscular Electrical Stimulation on Hospitalized Adults: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Age Aging*. 2023; 52(12): 1-13.

MUSICAL EXPERIENCE AND FRONTOTEMPORAL DEMENTIA

Studies have shown that musical experience can shape brain structure and function. The potential of music to modify the clinical expression of neurodegenerative brain pathologies has been largely unexplored. This study investigated the effect of past musical experience, current musical listening habits, and musical perceptual skills on the phenotypic expression of behavioral variant frontotemporal dementia (bvFTD).

The subjects were 14, consecutive patients with bvFTD seen at a national tertiary referral center in London. All underwent a comprehensive clinical, neuropsychological, and behavioral assessment, and had brain MRI assessments of atrophy. A control group included 29 demographically similar, healthy, older British adults. The patients' past musical experience and current musical listening habits were assessed using a structured survey, the Cambridge Behavioral Inventory-Revised (CBI-R). A caregiver completed an index of general neurobehavioral and psychiatric symptoms, as well as the Modified Interpersonal Reactivity Index (MIRI) of empathy and perspective taking.

Among patients with bvFTD, greater earlier life music experience was associated with better CBI-R scores ($p = 0.01$) and MIRI scores ($p = 0.03$). Past musical experience was not associated with performance on general neuropsychological tests (all $p > 0.05$). The number of hours per week currently listening to music was associated with sympathetic concern and MIRI total scores. Musical skills

were not associated with CBI-R or MIRI scores.

Conclusion: This study of patients with behavioral variant of frontotemporal dementia found that greater earlier life musical experience and current regular listening to music (but not musical processing skills) are significantly related to lower levels of socio-emotional behavioral disturbance.

Van't Hooft, J., et al. Musical Experience Influences Socio-Emotional Functioning in Behavioral Variant Frontotemporal Dementia. *Front Neurol*. 2024, January; 15: DOI:10.3389/fneur.2024.1341661.

LYSOPHOSPHOLIPIDS AND MILD TRAUMATIC BRAIN INJURY

The forces involved in a traumatic brain injury (TBI) can damage plasma membranes, triggering cellular molecular and neurochemical changes that can worsen neuropsychological outcomes. This study measured lysophospholipid metabolites in plasma samples from patients with mild TBI (mTBI), in an effort to determine whether altered levels were associated with outcomes.

The subjects were patients who presented to a level-one trauma center with an mTBI. All underwent blood sampling within 24 hours of injury, with metabolomics identifying 318 lipid metabolites for analysis. Each metabolite was compared between patients and a control group. Functional outcomes at discharge and at six months post-discharge were quantified using the Glasgow Outcome Scale-Extended (GOS-E), with scores characterized as good ($GOS-E \geq 7$) or bad ($GOS-E \leq 6$). The metabolites were compared with discharge and six-month GOS-E scores.

In the patients with mTBI, three metabolites were significantly increased, and 14 were decreased, as compared to controls. Regression models indicated that higher circulating levels of the lysophospholipids (LPL), 1-linoleoyl-glycerophosphocholine, 1-linoleoyl-GPE, and 1-linolenoyl-GPC, were associated with both good discharge GOS-E scores (odds ratio (OR) 12.2, 9.43 and 5.26 respectively) and good six-month GOS-E scores (ORs 4.67, 2.93, and 2.57 respectively).

Conclusion: This study of patients with mild traumatic brain injury found that higher plasma levels of LPLs (1-linoleoyl-GPC, 1-linoleoyl-GPE, and 1-linolenoyl-GPC) after

mTBI are associated with better functional outcomes at discharge and at six months post-injury.

Gusdon, A., et al. Lysophospholipids Are Associated with Outcomes in Hospitalized Patients with Mild Traumatic Brain Injury. *J Neurotrauma*. 2024, Jan; 41: 59-72.

CHRONIC PAIN, BIOMARKERS OF DEGENERATION, MICROGLIA, INFLAMMATION, AND COGNITIVE FUNCTION

Longitudinal studies have suggested that chronic pain is associated with cognitive decline and incident dementia. This study investigated the effect of chronic pain on cognitive function.

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, with subjects including adults with AD dementia, those with mild cognitive impairment, and healthy controls. All were classified using the ATN classification system (amyloid, tau, neurodegeneration). At each visit, the subjects were asked about pain symptoms, duration, and severity. Neuropsychological assessments included the composite scores of memory and executive function. Biomarkers of neurodegeneration included CSF concentrations of $A\beta_{1-42}$, ptau181, and t-tau. Neuroinflammation was assessed using CSF levels of soluble triggering receptor expressed on myeloid cells 2 (sTREM2), a marker of microglial activation and CSF inflammatory protein levels. Using predefined ATN biomarker cutoffs, four groups were identified. Two groups were identified along the AD continuum, those with biomarkers of degeneration (A+TN+) and those without (A+TN-). A third group was ATN negative and had suspected non-AD pathophysiology (SNAP); (A-TN+). The fourth group was ATN negative with normal biomarkers (A-TN-).

Data were reviewed for 995 individuals with a mean age of 73.07 years. Chronic pain was associated with inflammatory proteins in the CSF, although only in patients in the A-TN+ group. In that group, chronic pain was associated with increased CSF levels of sTREM2, a biomarker of microglial activation.

Conclusion: This study found that chronic pain is associated with neuronal damage, neurodegeneration, and microglial activation in patients with non-Alzheimer's disease pathology.

Sadlon, A., et al. Association of Chronic Pain with Biomarkers of Neurodegeneration, Microglial Activation, and Inflammation in Cerebrospinal Fluid and Impaired Cognitive Function. *Ann Neurol.* 2024; 95(1): 195-206.

GUT-MICROBIOTA-DERIVED METABOLITE TRIMETHYLAMINE N-OXIDE

Previous studies have demonstrated that gut microbiota may be involved in the onset or progression of Parkinson's disease (PD) and that those metabolites may be a central factor. Some have suggested that there may be an association between PD and Trimethylamine N-oxide (TMAO), which is produced by gut microbiota, although the data have been inconsistent. This study employed Mendelian randomization (MR) an epidemiological method that utilizes genetic variants to infer whether exposure (TMAO) and outcome (PD) are causally related.

Data were derived from published Genome Wide Association Studies (GWAS), using individuals of European descent. From these studies, single nucleotide polymorphisms (SNPs) representing genetic variations, were compared to metabolite concentrations. Those SNPs that demonstrated significant and independent associations with circulating levels of TMAO, betaine, carnitine and choline were extracted.

The MR analysis did not show the causal effects of TMAO, betaine, carnitine and choline on the risk of PD. However, suggestive evidence was observed that TMAO and its precursors may have a causal effect on PD progression. Genetically predicted higher TMAO was causally related to a reduced risk of motor fluctuation ($p=0.037$). Higher betaine was causally related to more advanced Hoehn and Yahr (HY) staging scale for PD ($p=0.004$) higher UPDRSIII scores ($p=0.002$) and increased risk of motor fluctuations ($p=0.039$).

Conclusion: This Mendelian randomization study employed the largest GWAS dataset of Parkinson's disease (PD) to demonstrate a suggestive, causal association between gut-microbiota-dependent metabolites and the progression of Parkinson's disease.

Zhou, H., et al. Causal Effect of Gut Microbiota Derived Metabolite Trimethylamine N-Oxide on Parkinson's Disease: A Mendelian

Randomization Study. *Euro J Neurol.* 2023;30(11):3451-3461.

INTERVENTIONS FOR FATIGUE IN PARKINSON'S DISEASE

Fatigue is a common symptom in patients with Parkinson's disease (PD). This literature review was designed to better understand the pharmacologic and behavioral options for the treatment of PD-related fatigue (PD-F).

A literature review was completed for randomized, controlled trials of medical or behavioral interventions for PD-F. From this review, 13 randomized, controlled trials were selected, with a total of 1,758 patients included in the analysis. Of the 13 studies chosen, six randomized, controlled trials focused on pharmacologic treatment, including two with amphetamines and four with dopaminergic drugs. Eight focused on behavioral therapy and six focused on exercise intervention. Outcome measures included the Fatigue Severity Scale (FSS) and the Parkinson's Fatigue Scale (PFS).

A group analysis revealed that improvement on the PFS was found with pharmacological interventions ($p=0.009$), but not with behavioral interventions ($p=0.06$). Improved PFS was found with high dose dopaminergic drugs ($p=0.009$), with less effect noted with low dose dopaminergic drugs ($p=0.06$). In a subgroup analysis of behavioral interventions, improvement on the PFS was noted with vestibular rehabilitation ($p<0.00001$), but not with exercise training ($p=0.29$).

Conclusion: This literature review of studies patients with Parkinson's disease found that fatigue was more improved with high dose than with low dose dopaminergic drugs and with vestibular rehabilitation but not exercise training.

Jiang, C., et al. Pharmacological and Behavioral Interventions for Fatigue in Parkinson's Disease: A Meta-Analysis of Randomized, Controlled Trials. *J Geriatric Psych Neurol.* 2023 Nov;36(6):487-495.

SHOCKWAVE THERAPY AFTER ACL RECONSTRUCTION

Anterior cruciate ligament reconstruction (ACLR) is a common treatment for patients with ACL rupture. As extracorporeal shockwave therapy (ESWT) is widely used as a treatment for musculoskeletal

disorders, this study explored the efficacy of radial ESWT (rESWT) as an adjunct therapy to rehabilitation after ACLR.

This randomized, single blind, clinical trial included adult patients undergoing unilateral ACL repair. All underwent standard progressive post-operative rehabilitation programs. Those randomized to the treatment group received daily rESWT beginning post-op day two. The control group underwent sham treatment. The rESWT included 2,500 impulses at 6-8 Hz to the treatment area, once per day for six weeks. Outcome measures included the visual analog scale for pain (VAS-P), Lysholm Knee Scores (LKS), range of motion (ROM) and the International Knee Documentation Committee (IKDC) scores.

Data were completed for 63 patients. Compared to the sham/control group, at three- and six-weeks follow-up, the rESWT group had more improved ROM, IKDC scores, Lysholm scores and VAS scores. At 24 weeks this difference was no longer apparent for any of the measures.

Conclusion: This study of patients undergoing surgical repair of an anterior cruciate ligament found that adding daily radial extracorporeal shock wave therapy to traditional rehabilitation resulted in faster improvement of pain and function scores at three and six weeks, with the differences resolving at 12 weeks.

Song, Y., et al. A Randomized Trial of Treatment for Anterior Cruciate Ligament Reconstruction by Radial Extracorporeal Shockwave Therapy. *BMC Musculoskelet Disord.* 2024, Jan 13;25(1)57.

CENTRAL SENSITIZATION AND NEUROPATHIC PAIN AFTER TOTAL KNEE ARTHROPLASTY

Approximately 20% of patients report being not satisfied with the results of a total knee arthroplasty (TKA). This study examined the relationship between central sensitization, neuropathic pain, and postoperative outcome.

This retrospective cohort study reviewed the medical records of consecutive TKAs performed at the author's institute between May 2019 and February 2023. Central sensitization was defined as a score of ≥ 40 on the Central Sensitization Inventory (CSI) with neuropathic pain defined as a score of ≥ 19 on the pain DETECT Questionnaire (PDQ).

(Continued from page 2)

*Preethika Venugopal, D.O.
Edward Chang, D.O.
Reilly Edmonds, OMS
Paulina Giacomelli, M.D.
Jake Gooing, D.O.
David Ho, D.O.
William Mendanha, D.O.
Eden Peykar, OMS
Riya Shah, D.O.
Max Zasuly, OMS, IV
UC Irvine, Irvine, CA

*Alwin David, M.D.
Shemar Crawford, M.D.
Sandra de Mel, M.D.
Robin Mata, D.O.
Univ. of Miami/JHS, Miami, FL

*Gurtej Singh Bajaj, M.D.
Peter Spurrell, M.D.
David Weinberg, M.D.
Univ of PA, Philadelphia, PA

*Joshua Wilson, M.D.
Christine Chilaka, M.D.
Univ. Of Washington, Seattle, WA

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 Bones and Brain in Review.**

Patient reported outcome was measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

Of the 132 patients in the study, 17.4% had both central centralization and neuropathic pain (Group 1), 21.5% had only central sensitization (Group 2), 11.1% had only neuropathic pain (Group 3), and 50% had neither condition (Group 4). Compared to group 4, the other three groups had worse scores on WOMAC, WOMAC pain and function ($p < 0.05$ for all comparisons). At two-year follow up, Group 1 had worse scores than the other groups for WOMAC, WOMAC pain and WOMAC function. Satisfaction with surgery ranged from 88% in Group 4 and 53.6% in Group 1.

Conclusion: This study of patients with end-stage OA treated with a total knee arthroplasty found that those who had preoperative central sensitization or neuropathic pain had a worse outcome than those who did not.

Kim, M., et al. Central Sensitization and Neuropathic Pain Cumulatively Affect Patients Reporting Inferior Outcomes Following Total Knee Arthroplasty *J Bone Joint Surg* 2024, Jan;106(2):102-109.

Bones and Brain in Review is produced monthly by physicians who specialize in Neuro-musculoskeletal medicine 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.

Private subscriptions are available by email at rehabinreview@aol.com or by fax or phone at (417) 779-9101. ISSN # 1081-1303



Produced by Emory University
School of Medicine



EXPANDING THE FRONTIER IN RESEARCH, TEACHING AND PATIENT CARE