

REHAB IN REVIEW

WWW.REHABINREVIEW.COM

TM

Volume 26 Number 6

Published by Physicians
In Physical Medicine and Rehabilitation

June 5, 2019

STROKE DYSBIOSIS INDEX IN GUT MICROBIOME

After a stroke, patients often display significant changes in the diversity of intestinal bacteria (microbiome), with increases in opportunistic pathogens and decreases in beneficial genera. As recent animal studies have demonstrated a correlation between gut microbiota and stroke outcome, this study used a human flora model to better understand this association.

Subjects included adult patients with a large artery atherosclerotic ischemic stroke. Stroke severity at baseline was assessed with the National Institutes of Health Stroke Scale (NIHSS). Medical data were gathered including fecal samples within 48 hours of admission. Fecal samples were obtained from 104 patients at admission and compared with 90 healthy controls. Eighteen genera were found to be significantly different between stroke patients and controls. A stroke dysbiosis index (SDI) was constructed to represent the relative difference in the 18 bacterial genera between patients with strokes and the controls.

The SDI of the stroke patients was positively correlated with NIHSS scores on admission ($p=0.034$), and modified Rankin Scale (mRS) scores at discharge ($p=0.004$). Patients with high SDI scores had significantly worse functional outcomes compared to those with low SDI scores ($p=0.004$). Among laboratory findings a logistic regression analysis found that the only independent predictors of unfavorable outcome were white blood cell count ($p=0.004$) and SDI ($p=0.011$). In a separate animal study, a stroke model was used to compare outcomes between mice implanted with High SDI and Low SDI bacteria. Those with high SDI had increased infarct volumes after ischemic lesions and increased pro-inflammatory cells compared to those with low infarct volumes.

Conclusion: This study found a significant difference in the fecal intestinal bacteria of patients with ischemic stroke compared with

controls. An animal study demonstrated that the replication of the stroke-associated bacteria pattern resulted in significantly greater infarct volume.

Xia, G., et al. Stroke Dysbiosis Index in Gut Microbiology are Associated with Brain Injury and Prognosis of Stroke. *Front Neurol.* 2019, April; 10:397.

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR TOBACCO ABUSE

Among those who attempt to quit smoking, over 60% relapse within the first two weeks. Only five percent succeed at one year. This study evaluated the effectiveness of transcranial direct current stimulation (tDCS) for the treatment of tobacco dependence.

This randomized sham-controlled parallel-group clinical trial included adults 15-65 years of age with addictions to nicotine, as defined by the DSM V criteria. The subjects were randomized to one of five groups including; A (300 mg bupropion), B (tDCS for 20 sessions over four weeks), C (sham tDCS for four weeks), D (tDCS for 20 sessions over 12 weeks), E (sham tDCS over 12 weeks). Stimulation intensity for the tDCS sessions was 2 mA for 20 minutes per session in the active group. The primary outcome was abstinence at six months, confirmed by salivary cotinine levels of <4 nanograms/ml.

Of the original group, 170 completed six months of the study. At six-month follow-up, successful tobacco cessation was achieved by 20% of group A, 5.7% of group B, 2.8% of groups C and E, and 25.7% of group D. Bupropion and tDCS treatments were both significantly better than the other groups ($p<0.001$). There was no significant difference between groups A and D ($p=0.26$).

Conclusion: This study found that transcranial direct current stimulation over 12 weeks was significantly more effective than a

shorter program and of similar efficacy to that of bupropion.

Behnam, S., et al. The Effects of Transcranial Direct Current Stimulation Compared to Standard Bupropion for the Treatment of Tobacco Dependence: A Randomized Sham-Controlled Trial. *Europ Psychiatry.* 2019, August; 60: 41–48.

STATIN USE AND RISK OF DEMENTIA AFTER CONCUSSION

While the majority of patients recover from a concussion within weeks, some develop lingering mood or neuropsychiatric disorders. As studies have suggested that statins may have neuroprotective effects, this study reviewed the effect of statin use on the risk of dementia among older adults with concussion.

This population-based multicenter double cohort study recruited subjects from April 1993 to April 2013. Patients were identified who were 65 years of age and older with a diagnosis of concussion. Those with a history of dementia or delirium in the prior five years were also excluded to reduce confounding from past neuropsychiatric conditions. Medical records were reviewed for a statin prescription within the 90 days prior to the concussion. Medical data were obtained including information about the concussion with the primary outcome being incident dementia.

Of the 28,815 patients diagnosed with concussion, 24.5% were prescribed a statin within 90 days of the concussion. In the four years after the concussion, 4,727 developed dementia. Statin use was correlated with a 13% reduced risk of dementia compared to those who did not use a statin ($p<0.001$). The relative reduction in dementia risk associated with statin use after a concussion was greatest for those taking rosuvastatin. No other cardiovascular or non-cardiovascular medications were associated with a decreased risk of dementia after a concussion.

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, EMBA, ALM
Harvard University, Cambridge, MA

Contributing Editors

* Benjamin Sirutis, M.D.

Hasan Abad, D.O.

Iain Bailey, M.D.

Natasha Bhatia, M.D.

John Hermansen, M.D.

Dana Norall, M.D.

Emory University, Atlanta, GA

*Anthony Mazzola, M.D.

Icahn Sch. of Med at Mt. Sinai, N.Y., NY

*Ethan Rault, M.D.

*Alex Richerand, M.D.

Steven D. Sanchez, D.O.

Eric Stockwell, M.D.

Zach Weilenman, M.D.

LSU Health Sci. Ctr., New Orleans, LA

*Alexander Sheng, M.D.

Ryan Doyel, M.D.

Debbie Lee, M.D.

N.W.U./R.I.C., Chicago, IL

* Kathy Plavnik, D.O.

* Kyle Seko, D.O.

Jordan Hui D.O.

Samantha Mastanduno, D.O.

Rosa Pasculli M.D.

Kyle Seko D.O.

NYU/Rusk Inst., New York, NY

* Dr. Michael Gallagher, M.D.

Ella D'Amico, M.D.

Jessica Sher, M.D.

German Valdez, M.D.

Rutgers-NJMS/Kessler, W. Orange, NJ

*Richard Lau, M.D.

Erin Barnes M.D.

David Oh, M.D.

Lorena Walker, M.D.

Temple University, Philadelphia, PA

* Marine Dididze, M.D.

University of Miami, Miami, FL

Conclusion: This study demonstrated that concussions are associated with long-term increased risk of dementia, which is reduced for patients who were taking a statin at the time of the injury.

Redelmeier, D., et al. Association between Statin Use and Risk of Dementia after Concussion. **JAMA Neurol.** 2019, May 20; doi:10.1001/jamaneurol.2019.1148.

BIOMARKERS FOR PREDICTING OUTCOME OF MILD TRAUMATIC BRAIN INJURY

Two biomarkers that have been studied in patients with brain injuries are glial fibrillary acidic protein (GFAP) an indicator of glial damage and almost exclusively found in the central nervous system, as well as neurofilament light (NF-L) protein, mainly expressed in the long myelinated white matter axons. This study was designed to assess the prognostic significance of these two biomarkers when measured soon after a mild traumatic brain injury (mTBI).

This prospective study included 107 adult patients with mTBI with blood samples obtained within 24 hours of emergency room arrival. TBI severity was assessed by the Glasgow Coma Scale Injury Severity score, duration of posttraumatic amnesia and CAT scans. Outcome was assessed at 6-12 months using the Glasgow Outcome Scale-Extended (GOSE), with recoveries defined as complete (GOSE 8), incomplete (GOSE <8), favorable (GOSE 5-8) and unfavorable (GOSE 1-4). The Rivermead Post-Concussion Symptoms Questionnaire was used to assess mTBI related symptoms.

Of the 107 patients recruited 55 were CT positive and 52 were CT negative. Patients with incomplete recovery had significantly higher levels of NF-L compared to those with complete recovery ($p=0.005$). There was a significant negative correlation between the levels of NF-L and GOSE scores ($p < 0.001$). For the prediction of complete recovery, the cut-off level of GFAP was 6438.05 pg/mL, with a sensitivity of 97% and a specificity of 26%. For predicting a favorable outcome, a cut-off value of GFAP was 12189.85 pg/mL, with a sensitivity of 92% and a specificity of 47%. For predicting complete recovery, the cut-off level of NF-L was 28.15 pg/mL, with a sensitivity of 94% and a specificity of 44%. For predicting a favorable outcome, the

cut-off value of NF-L was 53.6 pg/mL, with a sensitivity of 90% and a specificity of 67%.

Conclusion: This study of patients with a mild traumatic brain injury found that the levels of plasma GFAP and NF-L could be used to better predict complete recovery.

Hossain, I., et al. Early Levels of Glial Fibrillary Acidic Protein and Neurofilament Light Protein in Predicting the Outcome of Mild Traumatic Brain Injury. **J Neurotrauma.** 2019, May; 36(10): 1551-1560.

BIOMARKERS OF DELIRIUM IN ACUTELY ILL PATIENTS

Delirium affects up to 40% of hospitalized patients in general medical wards and is more frequent in the elderly. This literature review was designed to better understand the accuracy of several biomarkers in the prediction of delirium among acutely ill patients.

This review included studies that assessed delirium with the Confusion Assessment Method (CAM) for patients outside of the ICU, and the CAM-ICU for ICU patients. The search terms included delirium, cross referenced with terms such as biomarkers, inflammation, coagulation, endothelium, cytokines, chemokines, hormones, BDNF, RANTES, S100b, enolase, VCAM-1, ICAM-1, PDGF, TNF- α , neopterin, CRP, cortisol, and interleukin.

The literature search identified 69 articles published through April 2017, involving patients in 12 countries. Thirty inflammatory biomarkers were discussed in these manuscripts. The most commonly discussed were interleukin 6 (IL-6; 14 studies), C-reactive protein (CRP; 12 studies), IL-8 (10 studies), IL-10 (10 studies), IL-1 (8 studies), and tumor necrosis factor (TNF; 7 studies).

The data suggested that inflammatory markers, S100-Beta and cortisol, were correlated with an increased risk of delirium in hospitalized patients, and high levels of S100-Beta and CRP correlated with a higher risk of delirium during ICU stay.

Conclusion: This literature review found that the occurrence of delirium in hospitalized patients was associated with elevated inflammatory markers, S100-B and cortisol.

Michels, M., et al. Biomarker Predictors of Delirium in Acutely Ill Patients: A Systematic Review. **J**

OBESITY AND RISK OF DEMENTIA IN 65–74-YEAR-OLDS

Studies of the association between body mass index (BMI) and the risk of dementia have produced conflicting results, especially among patients over 65 years of age. This study was designed to better understand the association between BMI and dementia in patients 65–74 years of age.

Data were obtained from the Clinical Practice Research Data Link (CPRD) complete primary and secondary records for older populations in England. Records were reviewed from January 1, 2000 to November 17, 2014, including patients 65–74 years of age, with a BMI of 14–56.5 kg/m². Confounding comorbidities were recorded to assist with the analysis. Weight change over time was recorded.

Data were analyzed for 257,523 nonsmokers without a diagnosis of cancer, dementia, heart failure, or multi-morbidities. During the 15 years of follow-up, there were 9,774 incident cases of dementia and 29,466 deaths. During the first 10 years, obesity and overweight were inversely associated with incident dementia, with the hazard ratio (HR) for dementia for overweight and obesity of 0.65 and 0.74, respectively. From 10–15 years f/u, obesity was associated with an increased risk of dementia (HR 1.17).

Conclusion: This study of patients 65–74 years of age found a protective effect of overweight and obesity against dementia during the ensuing 10 years, which dissolved at 10–15 years.

Bowman, K., et al. Obesity and Longer-Term Risks of Dementia in 65–74-Year-Olds. *Age Ageing*. 2019, May; 48 (3): 367–373.

OBESITY PARADOX AND HIP FRACTURES

With the rise in obesity throughout the world many have expressed concern about the medical implications of this trend. However, several studies have reported that a high body mass index (BMI) is associated with improved survival among the elderly, especially those with certain chronic diseases. This study was designed to better understand the correlation between BMI and recovery after hip fracture.

Data were retrieved from a nationwide cohort study including patients 65 years of age and older treated for hip fracture during the years 2013–2016. Of those in the database, 36% had a BMI recorded. The patients were divided into four groups based on their BMI. These included; less than 22 kg/m², 20–25 kg/m², 25–30 kg/m² and over 30 kg/m². Mortality was determined by BMI group.

Subjects were 17,756 surgically treated hip fractures, including 60% women. The one-year survival for both men and women was greatest among those with a BMI of greater than 30kg/m², second among those with a BMI of 25–30kg/m², third among those with a BMI of 22–25 kg/m² and worst in those with a BMI of < 22kg/m². This trend was similar for both men and women. Compared to the normal weight category, the odds ratio for men returning to home four months after fracture was 1.4 for those with a BMI of > 30 kg/m², 1.38 for those with a BMI of 25–30 kg/m², and 0.63 for those with a BMI of <22 kg/m². The same trend was noted for women.

Conclusion: This study of elderly patients with hip fracture found that the one-year survival was greater among those with a higher BMI.

Karin, M., et al. Obesity Holds True for Patients with Hip Fracture: A Registry-Based Cohort Study. *J Bone Joint Surg*. 2019, May 15; 101 (10): 888–895.

RETURN TO WORK AFTER SHOULDER ARTHROPLASTY

With an aging population, an increasing number of shoulder surgeries are performed each year. Several studies have reviewed the return to work capacity of those undergoing such procedures. This systematic review and meta-analysis was completed to better understand this issue.

A data review was completed for studies of patients undergoing shoulder arthroplasty, which reported on return to work. Of those reviewed seven retrospective studies were chosen, representing data from 447 patients with a mean age of 63.6 years. Excluding those who were retired or not seeking employment before surgery, data from 317 patients were available for return to work analysis.

The overall return to work was 63.6% with a mean time out of work of 2.3 months. There was no difference in the rate of return to work

between arthroplasty surgery type. Return to work was significantly lower for patients with physically intense occupations (p=0.04). No significant difference was noted between those undergoing surgery for osteoarthritis, rotator cuff arthropathy, humeral fractures or by workers compensation status.

Conclusion: This study of patients undergoing shoulder arthroplasty found that 64% returned to work at an average of 2.3 months after surgery.

Steinhaus, M., et al. Return to Work after Shoulder Arthroplasty: A Systematic Review and Meta-Analysis. *J Shoulder Elbow Surg*. 2019, May; 28(5): 998–1008.

SLEEP APNEA AND PERIOPERATIVE COMPLICATIONS WITH SHOULDER ARTHROPLASTY

Epidemiologic studies have shown the incidence of sleep apnea (SA) have increased 15-fold in the past 17 years. As sleep apnea has been shown to be an independent risk factor for infection and revision procedures after spine and total joint arthroplasty, this study was designed to determine whether sleep apnea increases the odds of complications, as well as readmission rates among patients undergoing shoulder arthroplasty.

Data for the study were derived from a patient record database including over 100 million patients from various insurance databases covering orthopedic patients. Records from the Medicare Standard Analytic files from 2005–2014 were queried for patients with a diagnosis of SA undergoing primary total shoulder arthroplasty (TSA). Patients undergoing the same procedure without a diagnosis of SA served as controls. The 90-day medical, two-year implant related complications and 90-day readmissions as well as 90-day cost of care were compared between the two cohorts.

The SA group had a greater incidence of medical related complications compared with the control group (26% vs 12.3%; p<0.001). The two-year, short-term TSA-related complications were also greater in the SA group as compared to the control group (p<0.001). The 90-day readmission rate was similar between the two groups (p=0.828), though the 90-day costs were greater in the SA than in the control group (p<0.001).

Conclusion: This study of patients undergoing primary shoulder arthroplasty found that patients with a diagnosis of sleep apnea had a higher rate of medical complications and a higher cost of medical care.

Wang, C., et al. Perioperative Complications in Patients with Sleep Apnea Following Primary Total Shoulder Arthroplasty: An Analysis of 33,366 Patients. *J Orthop.* 2019, September-October; 16(5):382-385.

FIVE YEAR RISK OF STROKE AFTER INTRACEREBRAL HEMORRHAGE

Survivors of intracerebral hemorrhage (ICH) are thought to be at high risk of major vascular events with estimates ranging from 1.3%-27.4% per year. This study was designed to better understand the incidence of major vascular events in patients who survive an ICH.

This prospective study included patients from the Prognosis of Intracerebral Hemorrhage (PITCH) study, involving adults over 18 years of age, hospitalized between 2004 and 2009, with parenchymal hemorrhage. Patients who survived the first 30 days were included in the study. Patients were followed at six and twelve months and yearly thereafter. At each visit, researchers documented the occurrence of any symptomatic stroke or extracerebral vascular events since the last visit.

Of the 560 patients with spontaneous ICH (median age 70 years), 313 were alive at 30 days. At a median follow-up of six years, 82 patients had at least one major vascular event. Of these 57 were strokes (33 ischemic and 24 hemorrhagic). The cumulative incident rates of all types of ischemic events, including cerebral and extracerebral was 5.9% at one year and 15.2% at five years. The cumulative incidence rate of stroke was 7.1% at one year and 14.2% at five years. In a multivariable analysis, predictors of major ischemic events were ICH in a deep location, previous history of ischemic stroke and TIA, impaired renal function, diabetes, anticoagulant use at admission and a younger age.

Conclusion: This study of patients hospitalized with an intracerebral hemorrhage found that, of the 56% alive at 30 days, 15% had at least one major vascular event within five years.

Casolla, B et al. Five-Year Risk of Major Ischemic and Hemorrhagic

Events after Intracerebral Hemorrhage. *Stroke.* 2019, May; 50 (5) 1100-1107.

CATASTROPHIZING AND KNEE OSTEOARTHRITIS PAIN

Studies have demonstrated substantial variability in the pain of exercise for patients with chronic musculoskeletal pain, and that pain is one of the primary reasons for discontinuing exercise programs. As pain catastrophizing is an important predictive factor of pain, this study evaluated the effect of catastrophizing on the relationship between physical activity and daily knee pain in patients with knee osteoarthritis (KOA).

Subjects were 120 patients with advanced KOA, each awaiting unilateral total knee replacement. All were asked to complete self-report questionnaires, including demographics, psychosocial measures and pain related scales. Among the measures were the Pain Catastrophizing Scale (PCS), the WOMAC, the Godin-Shepherd Leisure-Time Physical Activity Questionnaire (GSLTPAQ), the Patient-Reported Outcomes Measurement Information System (PROMIS), a visual analogue scale for pain, the Six-Minute Walk Test (6 MWT) and a record of physical activity.

Higher PCS scores were significantly related to increased pain ($p < 0.001$). The relationship between physical activity and pain was moderated by catastrophizing ($p < 0.001$). Catastrophizing was significantly and negatively related to results of the GSLTPAQ ($p < 0.05$) and the 6 MWT ($p < 0.05$).

Conclusion: This study of patients with knee osteoarthritis found that increases in pain on days of heightened physical activity are more pronounced among patients with relatively higher levels of catastrophizing.

Lazaridou, A., et al. The Association between Daily Physical Activity and Pain among Patients with Knee Osteoarthritis: The Moderating Role of Pain Catastrophizing. *Pain Med.* 2019, May; 20(5): 916-924.

COMPARISON OF FIVE TREATMENT OPTIONS FOR PATELLA TENDINOPATHY

Patella tendinopathy, sometimes referred to as jumper's knee, is a chronic overuse injury of the patella

tendon. This study was designed to better understand the efficacy of common treatment options for this disorder.

The authors completed a secondary analysis of combined databases of three, randomized, controlled trials. The subjects were recruited through Dutch basketball, handball and volleyball associations. All studies were placebo controlled, with treatment options including eccentric training (ET), focused shockwave therapy (FSWT), radial shockwave therapy (RSWT), and topical glyceryl trinitrate (GTN). All subjects were assessed for pain function and sports participation with the Dutch VISA-P. Data were reviewed for 138 patients and compared by the treatment received. The primary outcome variable was clinical improvement, defined as an increase of 13 points or more on the VISA-P score after 12 to 14 weeks of treatment.

Of the 138 patients, 52 were "clinically improved" in VISA-P scores after three months of treatment. A multivariable logistic regression analysis demonstrated that both eccentric training alone ($p = 0.009$) and ESWT combined with eccentric training ($p = 0.015$) increase the chance for clinical improvement.

Conclusion: This combined analysis of three, placebo-controlled trials found that eccentric training alone or combined with extracorporeal shockwave therapy is effective for treating patella tendinopathy.

Van Rijn, D., et al. Comparison of the Effect of Five, Different Treatment Options for Managing Patellar Tendinopathy: A Secondary Analysis. *Clin J Sports Med.* 2019, May; 29 (3): 181-187.

ACUTE EXERCISE AND BREAKS IN SITTING ON MEMORY IN OLDER ADULTS

Dementia is associated with increased age as well as a number of modifiable risk factors. This study examined the effects of acute exercise with and without breaks in sitting on cognition among older adults at risk for developing dementia.

Subjects completed three conditions in random order with a six-day washout between conditions. These included uninterrupted sitting (SIT) for eight hours, sitting for one-hour, moderate intensity walking for 30 minutes, followed by uninterrupted sitting for 6.5 hours (EX + SIT), and

sitting for one hour, then moderate intensity walking for 30 minutes, sitting interrupted every 30 minutes thereafter, with three minutes of light intensity walking (EX+ BR), totaling 6.5 hours of sitting. Exercise was performed at 65-75% of age predicted maximum heart rate. The primary outcome measure was cognitive performance using a computerized test battery. Venous blood samples were collected to measure serum brain-derived neurotrophic growth factor (BDNF).

Sixty-five subjects completed all conditions. Relative to the SIT condition, memory was improved in the EC+BR condition ($p=0.04$). In addition, executive function was improved in the EX+SIT relative to the SIT condition ($p=0.03$). Serum levels of BDNF increased in both the exercise groups relative to the control.

Conclusion: This study involving elderly subjects found that a morning bout of moderate intensity exercise can improve working memory and executive function.

Wheeler, M., et al. Distinct Effects of Acute Exercise and Breaks in Sitting on Working Memory and Executive Function in Older Adults: A Three Arm, Randomized Crossover Trial to Evaluate the Effects of Exercise with and without Breaks in Sitting on Cognition. *Br J Sports Med.* 2019; 0: 1–7.

DIETARY SUPPLEMENTS AND MORTALITY

Recent studies have suggested that more than half of US adults report the use of dietary supplements, despite a lack of clear evidence the benefits of many of these. This study evaluated the association between dietary supplement use and all cause mortality.

Data were obtained from the National Health and Nutrition Examination Survey (NHANES), including those who had provided information concerning diet. Those who reported supplement used were asked about product name, frequency, duration and serving form. Estimates were made of the total daily dose of each supplemental nutrient. From the dietary reports, inadequate and excess nutrition intake was calculated. The outcomes were obtained through a link to the National Death Index.

Among the participants, 51.2% reported using dietary supplements in the previous 30 days. The most commonly used vitamin supplements

were vitamin C, vitamin E and vitamin D. The most commonly used mineral supplements were calcium, zinc and magnesium. More than half had inadequate dietary intake of vitamin D, vitamin E, choline, vitamin K and potassium. During a median follow-up of 6.1 years, 3,613 deaths occurred. A multivariable analysis found statistically insignificant associations for all supplements except for lycopene which was associated with lower risk of all cause death (relative risk 0.82) and cancer death (relative risk 0.66). Adequate intake of vitamin K and magnesium were associated with a lower risk of all cause death, though this reduction was associated with dietary and not supplement intake. Adequate intake of vitamin A, K, and zinc were associated with lower cardiovascular disease mortality, again restricted to dietary intake. Supplemental calcium intake of 1000 mg/d or higher was associated with an increased risk for cancer death.

Conclusion: This study found that supplement use was associated with a lower risk for all cause death, though these associations became insignificant after adjusting for education and lifestyle factors.

Chen, F., et al. Association Among Dietary Supplement Use, Nutrient Intake, and Mortality among US Adults: A Cohort Study. *Ann Intern Med.* 2019, May 7: 604–613.

SONOTHROMBOLYSIS FOR ACUTE ISCHEMIC STROKE

Sonothrombolysis is an ultrasound aimed at the residual flow and thrombus interface, shown in previous trials to increase the chance of early recanalization. This study was designed to establish the safety and therapeutic efficacy of sonothrombolysis combined with intravenous alteplase for the treatment of acute ischemic stroke.

This multicentered double-blind sham-controlled phase three randomized trial was conducted in 76 medical centers and 14 countries. Eligible patients were 18-80 years of age presenting with acute ischemic stroke who received intravenous alteplase within 3–4.5 hours of symptom onset. The patients were randomized either before or after the administration of the alteplase bolus to be treated with a therapeutic or sham sonothrombolysis activated within 30 minutes of the alteplase bolus and continuing for 120 minutes. The primary outcome was

improvement in the modified Rankin scale (mRS) scores at 90 days.

Between August 2013 and April 2015, 676 patients underwent randomization. The mRS did not differ between the two groups at 30 or 90 days. The study was discontinued after the secondary analysis demonstrated futility. The authors noted that the study did not require that a proximal occlusion be within the target area of the ultrasound device, producing a potential confounding factor. A follow-up study is underway to overcome this deficit.

Conclusion: This study of patients undergoing intravenous alteplase for acute ischemic stroke failed to demonstrate that sonothrombolysis could improve functional outcome.

Alexandrov, A., et al. Safety and Efficacy of Sonothrombolysis for Acute Ischemic Stroke: A Multi Center, Double-Blind, Phase 3, Randomized Controlled Trial. *Lancet Neurol.* 2019, April; 18(4):338–347.

VERUBECESTAT FOR PRODROMAL ALZHEIMER'S DISEASE

The amyloid hypothesis of Alzheimer's disease (AD) proposes that the accumulation of amyloid-beta in the brain triggers a spread of tau related neurofibrillary tangles, neural inflammation, and neuronal degeneration. Amyloid-beta ($A\beta$) is produced when amyloid precursor protein is cleaved sequentially by beta-site amyloid precursor cleaving enzyme (BACE). As Verubecestat, a BACE-1 inhibitor has been shown to reduce amyloid $A\beta$ this study assessed the effect of this medication in patients with prodromal AD.

Subjects were 50-85 years of age, with a subjective decrease in memory for at least one year, who scored at least one standard deviation below the mean on memory scores, with $A\beta$ evident on PET scan. The subjects were randomized to receive once daily oral verubecestat at a dose of 12 mg, 40 mg, or placebo. The primary efficacy outcome was the change from baseline to week 104 in the clinical dementia rating scale-sum of boxes (CDR-SB) score. Hippocampal volume on MRI was assessed at baseline and follow up.

Of the 1454 patients enrolled, 485 received the study drug at 12 mg and 484 at 40 mg per day. The $A\beta$ was reduced in both treatment groups as compared with placebo. However, the hippocampal volume loss was 6.1% in the placebo group and 6.7–6.5% in

the treatment groups. The mean change from baseline to week 104 in the CDR-SB scores was significantly worse in the 40 mg group than in the placebo group ($p = 0.01$). This pattern was also noted at weeks 13, 26 and 52. The study was discontinued for futility.

Conclusion: This study of patients with pre-Alzheimer's dementia found that while veribestat treatment reduced beta-amyloid, hippocampal shrinkage was worse, and some clinical measures of dementia were worse in the treatment group.

Eagan, M., et al. Randomized Trial of Verubecetate for Prodromal Alzheimer's Disease. *N Engl J Med*. 2019, April 11; 380:15:1408 -1420.

BODY MASS INDEX AND MORTALITY

Over the past decades, the prevalence of obesity has increased worldwide. While many studies have suggested that obesity increases the risk of several adverse health conditions, others have noted a J-shaped relationship between body mass index (BMI) and mortality, with the most favorable point on the curve being overweight or normal weight. This study applied mendelian randomization techniques to better understand the causal relationship between BMI and all-cause mortality.

Data were obtained from the Norwegian Nord-Trøndelag Health (HUNT) study and the UK Biobank. Subjects included 65,229 adults followed from 1995–1997 until April 2015. Data included BMI, self-administered questionnaires, and a physical exam, including genotyping. The UK Biobank includes 366,385 adults of European ancestry. The authors selected 77 single nucleotide polymorphisms as candidate instrumental variables for BMI based on European sex-combined analyses in a genome-wide association study of the GIANT (Genetic Investigation of Anthropometric Traits) consortium. Several mendelian randomization analyses were completed, assessing the association between genetically predicted BMI and mortality outcomes or disease incidence.

An increase of one unit in genetically predicted BMI was associated with a 5% higher risk of mortality in overweight patients, and a 9% higher risk of mortality in obese patients. Conversely, an increase of one unit in genetically predicted BMI was associated with a 34% lower risk in underweight and a 14% lower risk

in normal weight participants. In a subgroup analysis, a linear relationship between BMI and mortality was found in never smokers, with a J-shaped in ever smokers.

Conclusion: This study found that a J-shaped relationship between BMI and all-cause mortality was only evident among ever smokers with an always-increasing relation of BMI with mortality in never smokers.

Sun, Y., et al. Body Mass Index and All-Cause Mortality in Hunt and UK Biobank Studies: Linear and Non-Linear Mendelian Randomization Analyses. *BMJ*. 2019; 364:1042.

NICARDIPINE AND SHORT-TERM MORTALITY AFTER ISCHEMIC STROKE

While 75% of patients experiencing an ischemic stroke will have an acute hypertensive response, the optimal pharmacologic management within the first 72 hours remains controversial. The American Heart Association/American Stroke Association guidelines recommend nicardipine and labetalol as the two antihypertensive agents of choice. This study compared the short-term mortality in patients receiving one of these two drugs.

This retrospective analysis used data from a prospectively maintained database. Subjects included all patients with an admission diagnosis of ischemic stroke between November 2013 and January 2017. Data were retrieved for patients admitted to a neurocritical care unit including demographics, comorbidities, length of stay (LOS), as well as primary and secondary diagnoses.

Of the 244 patients, 42 (17.2%) received only labetalol, 25 (10.2%) received only nicardipine, and 33 (13.5%) received both. The overall in-hospital mortality was 7.8%. Among patients who received either antihypertensive agents, nicardipine was associated with a significantly higher mortality (7.4% versus 1.5%; $p < 0.04$). Among patients who received nicardipine, the mortality was 20% compared to 6.4% in patients who did not receive nicardipine ($p = 0.02$). In a logistic regression analysis, adjusting for comorbidities, nicardipine use remained associated with a higher risk of mortality (OR 4.6).

Conclusion: This study of patients hospitalized for ischemic stroke found that those treated with nicardipine had a higher risk of

mortality than those treated with labetalol.

Sadeghi, M., et al. Nicardipine Associated Risk of Short-Term Mortality in Critically Ill Patients with Ischemic Stroke. *J Stroke Cerebrovasc Dis*. 2019, May; 28(5): 1168-1172.

DYSPORT FOR CERVICAL DYSTONIA

Cervical dystonia (CD) is a painful, and potentially disabling condition characterized by abnormal head and neck postures, functional impairment, and reduced quality of life. As botulinum toxin injections have been successful in managing CD, this study compared the effects of injections of premixed abobotulinumtoxin A for injection (ASI), with injections of freeze dried, clinic mixed abobotulinumtoxin A (FD), for changes in dystonia and quality of life.

Subjects were adult patients with a diagnosis of CD and with a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score of ≥ 30 . Patients were randomized to receive 500 units of ASI, FD or a placebo. The patients were assessed for changes in spasticity, and for changes in the TWSTRS scores.

Of the 369 patients 156 received ASI, 159 received FD and 54 received placebo. Compared with placebo, quality of life, assessed by CDIP-58 total scores, was significantly improved at week four in both the ASI 500 U and the FD 500 U groups ($p < 0.0001$). A decrease in TWSTRS total score, was correlated with improvement in CDIP-58 total score. The effects of the two abobotulinumtoxin A arms were similar.

Conclusion: This study of patients with cervical dystonia found similar positive effects with the use of a premixed abobotulinumtoxin A to that of the traditional freeze dried-clinic mixed abobotulinumtoxin A.

Simonetta, M., et al. Quality Of Life Improvements in Patients with Cervical Dystonia Following Treatment with a Liquid Formulation of Abobotulinumtoxin A (Dysport). *Europ J Neurol*, 2019, June; 26 (6):943-947.

EVOLUTION OF SPASTICITY AFTER STROKE

After a stroke, the estimated prevalence of spasticity has ranged from 17-49%. This study was design

to better understand the prevalence and evolution at post-stroke spasticity during the first year after a stroke of carotid origin.

Subjects were consecutive patients with a primary stroke of carotid origin, and with motor deficits persisting at seven days. Study data included demographics, risk factors, medications, lesion location, motor deficits, spasticity and aphasia. Spasticity was measured with the modified Ashworth scale (MAS). The patients were examined at seven to ten days, six and 12 months following the onset of the stroke.

Of the 307 patients, 45% had spasticity at the seven to ten day evaluation. Severe spasticity (\geq MAS) was noted in 2.6%. The greatest prevalence and most severe spasticity was found in the elbow flexors of the contralateral limb. The highest rate of severe spasticity was noted at six month follow-up. A multivariable analysis found that the statistically significant predictors for absence/disappearance/decrease/no change in spasticity included a MAS of zero or one, a Barthel index of 100 and the use of muscle relaxants.

Conclusion: This prospective study of patients with stroke from carotid origin found that spasticity developed in almost half of the patients, with a rate of severe spasticity greatest at six months following stroke.

Dornak, T., et al. Prevalence and Evolution of Spasticity in Patients Suffering from First-Ever Stroke with Carotid Origin: A Prospective, Longitudinal Study. *Europ J Neurol*. 2019, June;26(6):880-886.

HIGH INTENSITY TRAINING AND HORMONE USE

Systemic inflammation is thought to adversely affect health. Among the factors that influence this inflammation are adiposity, physical activity and hormonal contraception. This study examined the influence of hormone contraceptive on changes in systemic inflammation after a 10 week course of strengthening and endurance training.

Subjects were women, 18-40 years of age, with a body mass index of less than 30 kg/m². Women were included who had at least one year of hormonal contraceptive use (HUC), as well as those who had never used hormonal contraceptives (NHC). All were involved in four high intensity training sessions per week, consisting of two strength training sessions and two endurance training sessions. All

subjects were assessed at baseline and after 10 weeks by performance measurements, and resting blood samples total cholesterol (Chol), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides, serum high sensitive C reactive protein (hs-CRP), Tumor-necrosis-factor- α (TNF- α), interleukin-6 (IL-6) and interleukin-1 β (IL-1 β). All measurements were made between one and five days of the menstrual cycle.

Compared to baseline, at 10 weeks, circulating concentrations of hs-CRP decreased significantly in the NHC group ($p=0.009$), and increased significantly in the HCU group ($p=0.048$). The between group difference was significant ($p=0.015$). Circulating TNF- α , IL-1 β , and IL-6 concentrations were unaffected by exercise with no between-group differences observed.

Conclusion: This study found that systemic inflammation, as measured hs-CRP, decreased after 10 weeks of intensive training among women who never used hormonal contraceptives, and actually increased among those using hormonal contraceptives.

Ihalainen, J., et al. Changes in Inflammation Markers After a 10-Week High-Intensity Combined Strength and Endurance Training Block in Women: The Effect of Hormonal Contraceptive Use. *J Sci Med Sport*. 2019. <https://doi.org/10.1016/j.jsams.2019.04.002>.

MENTHOL'S EFFECT ON EXERCISE PERFORMANCE

Menthol is a naturally occurring organic compound that invokes a range of biological responses. Recent studies have explored the non-thermal cooling properties of menthol for relieving thermal strain associated with exercise in the heat. This literature review and meta-analysis was designed to better understand the effects of menthol application on exercise performance and thermal sensation.

A literature review was completed for controlled studies involving exercise performance, thermal sensation and menthol. From this review, 13 articles were chosen which examined the effect of menthol on exercise performance. In these studies, menthol was applied via five different mechanisms including oral mouthwash, spray, cream/gel, drink, and immersion. In addition, 11 articles were included in a secondary

analysis examining effects of menthol on thermal sensation during exercise.

Overall, a small but significant improvement in exercise performance was found with menthol use compared to placebo ($p=0.05$). Comparing the methods of application, internal application produced a greater effect than did the other applications ($p=0.03$). In the secondary meta-analysis, a moderate to large reduction in thermal sensation during exercise was noted with menthol compared to control ($p<0.001$). In this analysis, external application including spray, cream/gel and immersion resulted in moderate to large effects ($p<0.001$), while internal applications produced small effects ($p<0.004$).

Conclusion: This literature review and meta-analysis found that menthol has a positive effect on exercise performance, with internal applications more effective than external.

Jeffries, O., et al. The Effects of Menthol on Exercise Performance and Thermal Sensation: A Meta-Analysis. *J Sci Med Sport*. 2019, June; 22(6):707-715.

CRYOTHERAPY AND SLEEP QUALITY

Exercise training during the evening has been shown to disrupt sleep patterns. As studies have suggested that cryostimulation may have an impact on sleep-onset latency this study assessed the effect of whole-body cryotherapy (WBC) on sleep quality after evening training in physically active men.

Subjects included 22 physically active men, who regularly engaged in one hour of exercise at least three times per week. Beginning at seven o'clock in the evening subjects engaged in a standardized training session for 55 minutes, and then underwent either a three-minute WBC session or a three-minute passive recovery session. Each session consisted of a five-minute warm up, followed by a continuous exercise bout at 65% MAS for 25 min and an intermittent exercise bout consisting of three sets of seven minutes at 85% MAS separated by two minutes of active recovery at 60% MAS. Those randomized to the WBC group spent 30 seconds at -25°C in the first chamber and then three minutes in the main chamber at -40°C . Subjects were assessed for perceived fatigue and pain before and immediately after exercise, as well as the next morning using a visual

(Continued from page 2)

*Vanessa Wanjeri, M.D.
Alyssa Marulli, M.D.
University of Penn., Philadelphia, PA

*Aileen Giordano, M.D.
Andrea Aguirre, M.D.
University of Va., Charlottesville, VA

*Amy Unwin, M.D.
Ashley Eaves, M.D.
University of Washington, Seattle, WA

*Michael Sookochoff, M.D.
Rahul Bijlani, M.D.
Michael Krill, M.D.
Sean Smith, M.D.
Washington U., 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.**

analog scale. Each night participants wore a wrist actigraph to assess sleep quality. Subjective sleep quality was recorded using the Spiegel Sleep Quality Perception Questionnaire (SSQPQ).

The actigraph demonstrated that the number of movements detected in the three spatial axes during sleep was significantly lower the night following WBC compared to the control condition ($p < 0.001$). The scores on the SSQPQ were significantly better in the WBC group than the passive recovery group ($p < 0.05$). Compared to evening fatigue and pain/muscle soreness, morning scores were significantly better in the WBC group than in the control group ($p < 0.01$).

Conclusion: This study found that a single session of whole-body cryotherapy after evening exercise can improve subjective and objective sleep quality and reduce perceived pain 24-hour after evening exercise in physically active men.

Douzi, W., et al. Three-Minute Whole-Body Cryotherapy/Cryostimulation after Training in the Evening Improves Sleep Quality in Physically Active Men. *Eur J Sport Med.* 2019; 19(6):860-867.

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 (800) 850-7388.
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