

# REHAB IN REVIEW

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## WHOLE GRAIN CONSUMPTION AND COGNITIVE DECLINE

Alzheimer's disease and related dementia (ADRD) affects more than six million Americans. Previous studies have suggested that adherence to certain foods is associated with a slower cognitive decline in older adults. This study investigated the association between whole grain consumption and changes in global cognition, perceptual speed, and episodic memory over time.

Data were obtained from participants in the Chicago Health and Aging Project (CHAP), a longitudinal, biracial, population-based study of Alzheimer's disease (AD) dementia and other health conditions among individuals  $\geq 65$  years of age. Every three years, the participants underwent an in-home assessment to collect information regarding demographics, health, function, and race. Each assessment included four cognitive functioning tests, consisting of two measures of episodic memory. Diet was assessed using a 144-item semiquantitative Food Frequency Questionnaire (FFQ) modified from the Harvard FFQ.

Data were reviewed for 3,326 participants with an average of three observations per person. An adjusted analysis revealed that, compared to those in the lowest quintile of whole grain consumption, those in the highest quintile had a slower rate of global cognitive decline ( $p = 0.004$ ), including perceptual speed ( $p=0.01$ ) and episodic memory ( $p = 0.02$ ). Those who consumed  $>3$  servings/d had a slower rate of decline in global cognition than did those who consumed  $<1$  serving/d.

**Conclusion:** This study found that whole grain consumption is associated with a slower rate of decline of global cognition, perceptual speed, and episodic memory.

Liu, X., Association of Whole Grain Consumption and Cognitive Decline: An Investigation From a Community-Based Biracial Cohort of Older Adults. *Neurol.* 2023, November 28; 101(22): E2277-E2287

## SEMAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITHOUT DIABETES

Overweight and obesity are independently associated with an increased risk of cardiovascular events. However, the clinical benefits of treating obesity to reduce the risk of cardiovascular complications remains uncertain. This study, the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, tested the clinical efficacy of this agonist of the glucagon-like peptide-1 (GLP-1) for reducing major, adverse, cardiovascular events among non-diabetic patients who are overweight and have cardiovascular disease.

The participants were 45 years of age or older and had a BMI of  $\geq 27$  kg/m<sup>2</sup>, with established cardiovascular disease. The patients were randomized to receive once weekly subcutaneous placebo or semaglutide at a dose of 2.4 mg. The primary cardiovascular endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.

During the study, 8,803 patients were assigned to receive semaglutide and 8,801 to receive a placebo. The mean reduction in body weight over the 104 weeks of the study was 9.39% in the semaglutide group and 0.88% in the placebo group. The primary cardiovascular endpoint occurred in 569 of the semaglutide patients (6.5%) and 701 (8%) of the placebo group ( $p < 0.001$ ). Death from cardiovascular causes occurred in 2.5% of the treatment group and three percent of the placebo group ( $p = 0.07$ ). Adverse events leading to permanent discontinuation of semaglutide, or the placebo occurred in 1,461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group ( $p < 0.001$ ).

**Conclusion:** This study of non-diabetic, overweight individuals with cardiovascular disease found that treatment with semaglutide could reduce the incidence of death from cardiovascular causes, nonfatal

myocardial infarction, or nonfatal stroke.

Lincoff, A., et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N Eng J Med.* 2023, Nov 11. doi: 10.1056/NEJMoa2307563. Epub ahead of print.

## PERIPHERIN AS BIOMARKER FOR PERIPHERAL AXONAL DAMAGE

Neurofilament light (NfL) is a widespread protein found in the neurons of both the peripheral nervous system (PNS) and the central nervous system (CNS). It belongs to the type IV intermediate filament group, forming part of the axonal cytoskeleton. The axonal cytoskeleton has three types of filament proteins; microtubules, microfilaments, and intermediate filaments, all of which are released with an axonal injury. Intermediate filaments are classified into five subtypes (I-V), of which peripherin is a type III intermediate filament protein, expressed almost exclusively in peripheral nerve axons. This study used single molecule array technology for the detection of serum peripherin as a biomarker for PNS axonal damage.

To assess the distribution of peripherin throughout neuronal and non-neuronal organs, immunostaining was employed, using anti-peripherin antibody and neurofilament light chain antibody. Peripherin levels were then measured by location and using models of primary axonal damage, primary demyelination, and controls. Longitudinal serum peripherin and NfL concentrations were compared within individuals with Guillain-Barré syndrome (GBS,  $n=45$ ), chronic inflammatory demyelinating polyradiculoneuropathy ( $n=35$ ), multiple sclerosis ( $n=30$ ), and dementia (as non-inflammatory CNS controls,  $n=30$ ), and healthy individuals ( $n=24$ ).

The authors found that NfL is present in the brain and spinal cord (CNS) and in the PNS. Peripherin is not measurably present in the brain,

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is detectable in the spinal cord and is most abundant in peripheral nerve axons. Peak peripherin levels were higher in the GBS group than in all other groups ( $p < 0.0001$ ). Peak NfL was highest in the GBS group (median 220.8 pg/ml) and lowest in healthy controls (median 5.6 pg/ml). However, NfL did not distinguish between CIDP (17.3 pg/ml), multiple sclerosis (21.5 pg/ml), and dementia (29.9 pg/ml). Peak NfL levels were higher with older age ( $p < 0.0001$ ).

**Conclusion:** This study found that a type III intermediate filament protein, peripherin, may be useful as a biomarker for acute peripheral nervous system damage.

Keddie, S., et al. Peripherin Is a Biomarker of Axonal Damage in Peripheral Nervous System Disease. *Brain*. 2023, November 2; 146 (11):4562-4573.

### PARTIAL MENISCECTOMY VERSUS PHYSICAL THERAPY FOR TRAUMATIC MENISCAL TEARS

Approximately 30,000 arthroscopic partial meniscectomies (APMs) are performed annually in the Netherlands. This study compared the economics of treating meniscal tears with physical therapy (PT) to that of treatment with APM.

Data were obtained from the Study of Traumatic Tears: Arthroscopic Resection versus Rehabilitation (STARR) trial. The subjects were 100 adults, 18 to 45 years of age, presenting with an MRI verified traumatic meniscal tear. The patients were randomized to receive APM or PT. Physical therapy consisted of a standardized exercise program and home exercises. The number of quality-adjusted life years (QALYs) during the 24-month follow-up was determined using the EuroQol five-dimension three-level health questionnaire (EQ-5D-3L). Healthcare costs and lost productivity were calculated for each group.

During the two-year study, the health care costs were 3,645 euros (€) in the surgery group and €2,881 in the PT group. As 41% of the patients that were randomized to the PT group eventually underwent surgery during the follow-up period, €2,165 of the €2,881 of the PT group cost were costs accrued from surgery. Productivity costs (losses) were €6,037 in the APM group and €5,778 in the PT group. The EQ-5D-3L scores improved substantially over time and did not differ significantly between the groups.

**Conclusion:** This randomized, controlled trial of patients with

traumatic meniscal injury found that, compared to conservative treatment with physical therapy, surgical treatment was more costly and resulted in a greater loss of productivity, with no benefit in quality of life.

Van der Graaff, S., et al. Cost Effectiveness of Arthroscopic Partial Meniscectomy versus Physical Therapy for Traumatic Meniscal Tears in Patients Aged Under 45 Years. *Bone Joint J*. 2023, Nov 1;105-B(11):1177-1183.

### GASTROINTESTINAL INFLAMMATION AND NEURODEGENERATIVE DISEASE

Diseases of the gastrointestinal (GI) system have been linked to a subsequent risk of Alzheimer's disease (AD) and Parkinson's disease (PD). As the most frequent histological findings of GI endoscopy are normal histological (NM) features and inflammatory histological changes not categorized as inflammatory diseases [nonspecific inflammation, (NSI)], this study assessed the association between NM or NSI among patients who underwent biopsies as part of a workup for GI symptoms.

The ESPRESSO study is a nationwide matched cohort study of individuals with any GI histopathological record available from Sweden's 28 pathology departments during 1965 through 2016. Those with NM ( $n=480,346$ ) or NSI ( $n=655,937$ ) were matched with up to five controls. All were followed until an incident diagnosis of AD or PD, emigration, death, or the end of the study. The matched controls were compared to those with NM or NSI (exposed group).

During a mean follow-up time of 12 years, compared to controls, those with normal mucosa had a higher risk of AD (hazard ratio (HR) 1.15) and PD (HR 1.16). The corresponding HRs for those with nonspecific inflammation for the risk of AD and PD were 1.11 and 1.10. The exposed group had a constantly higher cumulative incidence rate of AD and PD from two years after biopsy onward. A higher risk of vascular dementia and other dementias was also noted among the exposed individuals.

**Conclusion:** This matched cohort study found that patients presenting with GI symptoms, but with biopsy results of normal mucosa or nonspecific inflammation had an elevated risk of incident Alzheimer's disease or Parkinson's disease, suggesting that GI symptoms may be

a harbinger for these diseases.

Sun, J., et al. Gastrointestinal Biopsy of Normal Mucosa or Nonspecific Inflammation and Risk of Neurodegenerative Disease: Nationwide Matched Cohort Study. *Euro J Neurol*. 2023, November; 30 (11): 3430-3439.

### SKELETAL MUSCLE LOSS AFTER FEMORAL FRAGILITY FRACTURE

After a femoral fragility fracture, immobilization and nutritional deficiency may lead to further loss of skeletal muscle mass secondary to the catabolic response to injury. This study was designed to better understand the changes in skeletal muscle mass after such a fracture.

The subjects were 71 adults, 65 years of age or older, treated with operative fixation of an isolated femoral fragility fracture. Body composition was measured using bioelectrical impedance analysis (EIA) of the trunk, arms, and legs. Total body weight, body mass index, and appendicular skeletal mass index were recorded within 72 hours of admission, and up to six months after discharge. Covariates included age, gender, tobacco use, the modified Frailty Index, preinjury use of an assistive device for ambulation, preinjury assistance in activities of daily living, discharge disposition, and fracture type.

Skeletal muscle mass measurements demonstrated a nine percent loss between the time of injury and six weeks after injury ( $p < 0.001$ ). The lost muscle mass had not recovered at three months after injury. While there was a slight recovery between three- and six-months post-injury, that difference was not significant.

**Conclusion:** This study of older adults with femoral fragility fractures found that patients lost a substantial amount of skeletal muscle mass and physical function within the first six weeks, which did not recover by six months.

Willey, M., et al. Substantial Loss of Skeletal Muscle Mass Occurs after Femoral Fragility Fracture. *J Bone Joint Surg*. 2023, Nov 15; 105(22): 1777-1785.

### NUTRITIONAL SUPPLEMENTATION IN OLDER ADULTS WITH HIP FRACTURES

Hip fractures in older patients are associated with a significant risk of postoperative complications and prolonged hospital stays. Malnutrition,

a common issue in this population, further exacerbates these risks. This systematic review and meta-analysis assessed the potential benefits of oral nutritional supplements (ONS) in improving postoperative outcomes in this group.

A literature search was completed for publications through August 30, 2022. The inclusion criteria were age 50 years or older, hip fractures, and use of high protein-based diet strategies, with or without added nutrients. The outcome measures were hospital length of stay and functional outcome.

Data were included from 1,522 patients from 18 randomized, controlled trials. Those patients randomized to receive ONS had significantly increased elevated albumin levels (weighted mean difference (WMD) 1.24 as well as a significant risk reduction in infective complications (odds ratio (OR) 0.54) pressure ulcers (OR 0.54) and total complications (OR 0.57). In addition, hospital length of stay (LOS) was also significantly reduced (WMD -2.36) particularly in rehabilitation LOS (WMD -4.17). The ONS group had a lower mortality risk (OR 0.93) and readmission (OR 0.52), though these did not reach statistical significance.

**Conclusion:** This study found that that ONS could nearly halve the risk of infective complications, pressure ulcers, total complications, as well as improve serum albumin and reduce hospital length of stay.

Chen, B., et al. Effect of Oral Nutritional Supplementation on Outcomes in Older Adults with Hip Fractures and Factors Influencing Compliance. *Bone Joint J*. 2023, November 1; 105-B(11):1149-1158.

### PARKINSON'S DISEASE AND INTESTINAL ALTERATIONS

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disease of the central nervous system, characterized by motor and non-motor symptoms. This study assessed patients with PD for changes in fecal microbiota composition, alterations, inflammatory markers in the blood and stool, and changes in the colonic mucosal barrier.

The subjects were 19 patients diagnosed with PD and 19 asymptomatic, matched controls. Intestinal permeability was assessed using levels of lipopolysaccharide binding protein (LBP). Other blood tests included levels of thyroid-stimulating hormone (TSH), C-reactive protein, interleukin-1 $\beta$  (IL-

1 $\beta$ ), and tumor necrosis factor (TNF). Stool sampling was performed to measure *helicobacter pylori* antigen (Ag), fecal calprotectin, IL-1 $\beta$ , and TNF levels. The integrity of the intestinal barrier was assessed by biopsy.

Compared to controls, those with early PD demonstrated decreased LBP levels, while those with late PD demonstrated increased LBP levels. Plasma and fecal TNF levels as well as fecal IL-1 $\beta$  levels were increased in the patients with PD compared to controls. The histology of the biopsied tissue identified a decrease in epithelial neutral mucins and claudin-1 expression, as well as an increased expression of acidic mucins, collagen fibres, and S100-positive glial cells.

The fecal analysis found that, compared to controls, those with PD had less abundance of *rhodoluna*, *butyricimonas*, and *caulobacteraceae*, and a greater abundance of *parabacteroides*, *tannerellaceae*, *eubacterium eligens*, *eubacterium ruminantium*, *peptococcaceae*, *negativibacillus*, *ruminococcaceae* and *variovorax*.

**Conclusion:** This small study found that patients with Parkinson's disease have altered populations of the intestinal microbiome, impaired mucosal barrier, increased enteric inflammation and profibrotic remodelling of the colonic mucosa.

Bellini, G., et al. Intestinal Histomorphological and Molecular Alterations in Patients with Parkinson's Disease. *Europ J Neurol*. 2023, November; 30(11): 3440-3450.

### GAIT SPEED AND MULTIPLE SCLEROSIS PROGRESSION

The rate of progression among patients diagnosed with multiple sclerosis (MS) varies among individuals and phenotypes. Earlier studies have not successfully predicted the rate of progression in relapse-remitting or primary progressive MS patients. This prospective, observational study evaluated whether a baseline six-minute walk test (6MW) could distinguish between MS patients with high or low risk of worsening of their disease over two years.

Participants were 62 patients with MS and 41 healthy controls (HC), 18 to 64 years of age. At baseline, demographics, smoking exposure (by pack-years), medical history, and medications were documented. The MS-related disability was assessed using the Expanded Disability Status Scale (EDSS). The six-minute walk

test (6MWT) was evaluated, minute by minute, using a surveyor's measuring wheel. A fitted growth mixture model (GMM) was used to identify unobserved subpopulations. Disease progression over 24 months was documented for each subject.

At baseline both MS groups walked significantly slower than HC with a baseline difference of 23 feet/min for LRP ( $p = 0.009$ ) and 106 feet/min for HRP ( $p < 0.001$ ). The HRP subgroup demonstrated a "U" shape, marked by an acceleration in the final minutes of the 6MW. The other MS subgroup had a slower gait speed and a distinct "flattened" 6MW gait speed trajectory curve. When compared from baseline to 24 months follow up, the HRPs had a significant worsening of 6MW gait speed, the LRPs demonstrated no significant worsening, and the HCs demonstrated an improvement (increased speed).

**Conclusion:** This study of patients with MS found that a minute-by-minute evaluation of the baseline six-minute walk test was helpful in identifying subgroups with different risks of disease worsening over time.

Goldman, M., et al., Progression Risk Stratification with Six-Minute Walk Gait Speed Trajectory in Multiple Sclerosis. **Front Neurol.** 2023; 14:1259413.

### **MENIERE'S DISEASE, BETAHISTINE, AND TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION**

Meniere's disease is defined by spontaneous vertigo, low to mid-frequency hearing loss, and tinnitus. These individuals are at increased risk for falls and further loss of independence. This study assessed the efficacy of a combination of transcutaneous auricular vagus nerve stimulation (taVNS) and betahistine mesylate for the relief of symptoms and improvement quality of life of patients with Meniere's disease.

The single-center study included 92 patients diagnosed with Meniere's disease, 18 to 65 years of age. All subjects received betahistine mesylate, 6mg three times per day, and were randomized to receive taVNS or a placebo. The primary outcome measures were the Tinnitus Handicap Inventory (THI), Dizziness Handicap Inventory (DHI), Pure Tone Auditory (PTA), and a visual analogue scale (VAS) of aural fullness.

At 12 weeks, the taVNS group scored better than the control group on the THI ( $p < 0.001$ ), DHI ( $p < 0.001$ ), VAS of aural fullness ( $p < 0.01$ ), pure

auditory fullness ( $p < 0.001$ ), and PAT ( $p < 0.001$ ). At 12 weeks, improvement in quality of life, measured with the SF-36, was greater in the taVNS group than in the control group ( $p < 0.001$ ).

**Conclusion:** This study of patients with Meniere's disease found that combining betahistine mesylate with transcutaneous vagus nerve stimulation at the ear could improve symptoms and quality of life.

Wu, D., et al. Meniere's Disease Treated with Transcutaneous Auricular Vagus Nerve Stimulation Combined with Betahistine Mesylate: A Randomized, Controlled Trial. **Brain Stimul.** 2023, Oct 13; 16(6): 1576-1584.

### **COLLAGENASE TREATMENT DECREASES MUSCLE STIFFNESS IN CEREBRAL PALSY**

Recent studies have shown that the stiffness of muscle fiber bundles among children with cerebral palsy (CP) is associated with increased collagen in the extracellular matrix, rather than the muscle fibers themselves. *Clostridium histolyticum* (CCH) is a selective collagenase that lyses types I and III collagen while preserving type IV collagen. This study tested the effects of CCH on muscle stiffness and range of motion in patients with CP.

Muscle biopsies from 11 patients with spastic CP were obtained at the time of surgery. The samples were treated with zero, 200 units per ML, 350 units per ML, or 500 units per ML of CCH. After treatment, the samples were assessed for the percentage of collagen reduction. A biomechanical testing apparatus was used to assess muscle stiffness, before and after incubation in a CCH bath.

The reduction in collagen content increased with increasing CCH dose. The median decrease in collagen from before to after CDC treatment was 27%. After CCH treatment, muscle stiffness was reduced significantly ( $p = 0.003$ - $p = 0.004$ ). No significant reduction in protein content was detected after CCH treatment.

**Conclusion:** This study using muscles biopsied from patients with spastic CP found that *clostridium histolyticum* can reduce collagen content and decrease stiffness, without muscle deterioration.

Howard, J., et al. Collagenase Treatment Decreases Muscle Stiffness in Cerebral Palsy: A Preclinical, *Ex Vivo*, Biomechanical Analysis of Hip Adductor Muscle Fiber Bundles. **Dev Med Child Neurol.** 2023, December; 65(12):

1639-1645.

### **PULSED RADIOFREQUENCY IN PERSISTENT SPINAL PAIN SYNDROME**

Persistent Spinal Pain Syndrome (PSPS), formerly referred to as Failed Back Surgery Syndrome (FBSS), is a unique medical condition that is marked by radicular neuropathic leg pain, sometimes combined with low back pain. The use of Pulsed Radiofrequency (PRF) is a common procedure to treat PSPS, but its success rate in relieving pain, when an electrode is inserted through the sacral hiatus, has been suboptimal. To enhance the outcomes, a new configuration was developed to provide a more efficient distribution of the relevant electric fields. This was named Optimization Current Flow (OCF). This study assessed the efficacy of this procedure for patients with PSPS.

Ten patients with PSPS were treated with PRF using the OCF configuration. Delivery was provided through a steerable epidural catheter with a reference electrode positioned outside the foramen. The duty cycle of PRF was  $2 \times 10$  msec, and the total exposure time was 150 seconds. Follow-up assessments were conducted at one, three, and six months.

Success was defined as an improvement of three points or more on the Numerical Rating Scale (NRS). The NRS scores improved from a preoperative median score of eight to a median of 3.9 post-treatment. A successful treatment outcome was noted in 69% of the patients.

**Conclusion:** This pilot study of patients with persistent spinal pain syndrome found that the Optimization Current Flow configuration for pulse radio frequency was successful in more than half of patients in reducing pain.

Dario, A., et al. The Treatment of Persistent Spinal Pain Syndrome with Epidural Pulsed Radiofrequency: Improvement of the Technique. **Frontiers In Neurol.** 2023, Oct 16; 14: 1236270.

### **NON-SURGICAL TREATMENT OF THUMB OSTEOARTHRITIS**

The prevalence of symptomatic osteoarthritis (OA) of the thumb is estimated to be seven percent in females and two percent in males. With the aging of the population, these numbers are expected to rise. Most guidelines for the management

of this disease suggest nonsurgical treatment, such as the use of an orthosis, medications, or exercise. This study compared the pain and limitations in activities of daily living among those treated with surgery and those treated conservatively.

Participants were patients diagnosed with carpometacarpal OA by hand surgeons. All subjects had been referred for hand therapy between January of 2011 and October of 2015. Conservative treatment was based on the local and Dutch treatment guidelines, generally consisting of the use of a custom-made or prefabricated orthosis, weekly 25-minute therapy sessions, including exercises and education to achieve a more stable opposition position, and daily exercises. The primary outcome variables were changes in pain and limitations in ADL between 12 months and more than five years. Pain was assessed with a visual analog scale (VAS) at rest and during activities. Function was measured with the Michigan Hand Outcomes Questionnaire administered at baseline and three months' follow-up.

Scores on the Michigan Hand Outcomes Questionnaire (MHQ) Pain subscale did not change between 12 months and five years, while the scores on the ADL subscale improved by 4.4 points, reaching statistical but not clinical significance. At follow-up, 16% rated their results as excellent and 39% as good. Conversion to surgery at seven years had occurred in 22% of the patients, with 70% of these occurring in the first year.

**Conclusion:** This study of patients with osteoarthritis of the thumb found that treatment with conservative treatment, pain and limitations in activities of daily living did not worsen after 12 months.

Lopez, L., et al. Long-Term Outcomes of Nonsurgical Treatment of Thumb Carpometacarpal Osteoarthritis. A Cohort Study. *J Bone Joint Surg Am.* 2023, October 30: [Http://Dx.Doi.Org/10.2106/JBJS.22.01116](http://dx.doi.org/10.2106/JBJS.22.01116).

### BONE MORPHOGENIC PROTEIN SIGNALING AND OSTEOARTHRITIS

Despite the rapidly increasing global prevalence of osteoarthritis (OA), disease modifying treatments remain elusive. Recently, researchers discovered the Distal Proliferative Zone (DPZ), an area of bipotential proliferating cells, which is under the influence of bone morphogenetic protein (BMP) signaling. As studies have shown that

ectopic activation of BMP signaling results in transient cartilage differentiation, the authors hypothesized that BMP signaling-induced transient cartilage differentiation may be the molecular basis for the pathogenesis of OA. This study analyzed the effect of BMP signaling induced cartilage differentiation as an essential molecular element of the pathogenesis of OA.

Adult mice underwent anterior cruciate ligament (ACL) surgery to induce OA. To activate BMP signaling, tamoxifen was injected into the intraperitoneal cavity. To block BMP, the animals received an intra-articular injection of LDN-193189. The mice were followed using micro-CT, histological staining, and immunohistochemistry to assess for signs of OA progression.

Micro-computed tomography ( $\mu$ CT) structural examination found that the ACLT + placebo group had extensive damage to articular surfaces, as well as osteophyte formation. In the studies that blocked the BMP using LDN-193189 injections, the phenotypic and molecular changes of OA development were significantly curtailed following ACL transection. When the intra-articular LDN-193189 injections were delayed until post-surgery day 35, the phenotypic and molecular changes of OA were reduced, but not to the extent of those treated pre-onset of OA.

**Conclusion:** This animal study suggests that BMP signaling is necessary and sufficient in the pathogenesis of OA.

Jaswal, A., et al. BMP Signaling: A Significant Player and Therapeutic Target for Osteoarthritis. *Osteoarthr Cartil.* 2023, November; 31(11): 1454-1468.

### POST-TRAUMATIC OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT REPAIR

Anterior cruciate ligament (ACL) injuries are frequently treated by operative repair. Despite the short-term outcomes, these surgeries are associated with an increased risk of post-traumatic osteoarthritis (PTOA). As surgical techniques have evolved over the past decades, this study was designed to better understand the prevalence of PTOA after ACL repair, to determine whether this prevalence has decreased over time.

This systematic review included studies of ACL repair published between January of 1980 and May of 2022, involving a total of 11,818

patients. The articles chosen had at least a 10-year follow-up.

At a median follow-up of 14.6 years, the prevalence of PTOA in the operative knee was 38.4%. The pooled prevalence of PTOA was high within each follow-up duration, and PTOA was present in over 50% of the patients after 20-year follow-up. The meta-analysis found that the prevalence of PTOA after surgery for ACL injury decreased only slightly or not at all over the years of the study.

**Conclusion:** This literature review and meta-analysis of patients undergoing anterior cruciate ligament repair found that the prevalence of osteoarthritis after these surgeries has not decreased over time, despite improvements in surgical repair techniques.

Liukkonen, R., et al. Prevalence of Post-Traumatic Osteoarthritis after Anterior Cruciate Ligament Injury Remains High, Despite Advances in Surgical Techniques. *Bone Joint J.* 2023; 105-B (11): 1140-1148.

### LECANEMAB FOR EARLY ALZHEIMER'S DISEASE

While current therapeutic agents for Alzheimer's disease (AD) related dementia may temporarily improve symptoms, they do not seem to alter the underlying course of the disease. Lecanemab is a humanized monoclonal antibody that binds with high affinity to soluble amyloid-beta ( $A\beta$ ) protofibrils. This study was designed to determine the safety and efficacy of this medication for the treatment of patients with early AD.

This 18-month, multicenter, double-blind, placebo-controlled, parallel group trial included patients 50 to 90 years of age, diagnosed with early AD (mild cognitive impairment (MCI) or mild dementia due to AD) with evidence of amyloid in the cerebrovascular fluid or seen on positron-emission tomography (PET). The patients were randomized to receive IV lecanumab, 10 mg/kg every two weeks, or a placebo. Amyloid positivity was determined by PET or CSF measurement of  $A\beta$ 1-42. The primary efficacy endpoint was the change in the score on the Clinical Dementia Rating scale's sum of boxes (CDR-SB), from baseline to 18 months.

Data were analyzed from the records of 898 patients in the treatment group and 897 in the control group. The mean changes from baseline to 18 months in the CDR-SB score were 1.21 in the treatment group and 1.66 in the placebo group ( $p < 0.001$ ). In a substudy of amyloid burden on PET, the

adjusted mean changes from baseline at 18 months were -55.48 centiloids in the lecanemab group and 3.64 centiloids in the placebo group ( $p < 0.001$ ). The adjusted mean changes from baseline at 18 months in the ADAS-cog14 score were 4.14 in the lecanemab group and 5.58 in the placebo group.

**Conclusion:** This phase III trial of lecanemab for patients with early Alzheimer's disease found that this medication could reduce the progression of amyloid deposit and cognitive deterioration.

van Dyck, C., et al. Lecanemab in Early Alzheimer's Disease. *N Eng J Med.* 2023, January 5; 388(1):9-21.

### LONGER-TERM EFFECT OF MODEL OF CARE FOR OSTEOARTHRITIS

Between 2010 and 2019 the number of people in the world with osteoarthritis (OA) rose by 28%, with the prevalence expected to continue to rise due to the aging of the population and increased obesity. Despite available treatment recommendations, the majority of patients with OA do not receive recommended core treatment modalities. This study was designed to assess the quality-of-care effectiveness and cost effectiveness of the SAMBA structured model of care for hip and knee osteoarthritis.

Three hundred ninety-three subjects were recruited from adults living in six municipalities in Norway between January of 2015 and October of 2017. The participating general practitioners (GPs;  $n = 40$ ) and physical therapists (PTs;  $n = 37$ ) identified adults aged  $\geq 45$  years with symptomatic hip or knee OA. The treatment was a PT led, OA patient education program followed by an eight- to 12-week exercise program, with one-hour supervised group sessions twice a week. Resistance exercise was increased to 60 to 70% of the one repetition max. The patients were encouraged to add a third, home-based session. An optional 10-hour healthy eating program was also available at Healthy Life Centers. The primary outcome measure was the Osteoarthritis Quality Indicator.

At 12 months, the intervention group reported statistically significantly higher Osteoarthritis Quality Indicator scores as compared to the control group. Cost-effectiveness analyses showed that the model of care resulted in quality-adjusted life-years gained.

**Conclusion:** This study of adults with OA of the knee or hip found that

implementing core recommendations through a structured model of care in primary healthcare result in better quality of care with less cost than traditional care.

Osteras, N., et al. Longer-Term Quality of Care, Effectiveness, and Cost Effectiveness of Implementing a Model of Care for Osteoarthritis: A Cluster Randomized, Controlled Trial. *Osteoarthr Cartilage.* 2023, Oct 13:S1063-4584(23)00946-9.

### HERBAL-BASED TREATMENT FOR SEPSIS

Sepsis is caused by a dysregulated inflammatory response to infection and remains one of the leading causes of mortality worldwide. Xuebijing injection (XBJ) is an herbal based intravenous preparation designed to treat sepsis and multiple organ dysfunction syndrome. This study was conducted to determine the efficacy and adverse effects of XBJ for patients with sepsis.

The Efficacy of Xuebijing Injection in Patients with Sepsis (EXIT-SEP) trial was a randomized double-blind placebo-controlled multicenter parallel group trial, conducted in intensive care units at 45 sites across China. The subjects were adult patients 18 to 75 years of age with a diagnosis of sepsis with Sequential Organ Failure Assessment (SOFA) scores of two to 13. The patients were randomly assigned to receive 100 milligrams of XBJ mixed with 100 mL of normal saline every 12 hours or a matched placebo for five consecutive days. The investigators followed local sepsis management guidelines and the international guideline for management of sepsis and septic shock. The primary outcome was all cause mortality, 28 days after randomization.

During the study, 911 patients were allocated to receive either XJB twice per day and 906 to receive placebo plus standard of care. The 28-day mortality rate was 26.1% of the placebo group and 18.8% of the XBJ group ( $p < 0.001$ ). In a subgroup analysis, the difference in 28-day mortality rates between the groups was 7.6 percentage points among those with a baseline SOFA score of 2-7 and 6.8% among the patients with baseline sofa scores of 8-13. At least one adverse event was noted in 24.1% of the treatment and in 25.3% of the placebo groups within 28 days.

**Conclusion:** This large scale randomized clinical trial of patients hospitalized with sepsis found that the herbal treatment XBJ at a dose of 100mL every 12 hours, resulted in a

significant reduction in mortality.

Liu, S., et al. Effect of An Herbal Based Injection on 28 Day Mortality in Patients with Sepsis. The EXIT-SEP Randomized Clinical Trial. *JAMA Intern Med.* 2023, Jul 1;183(7):647-655.

### GREATER OCCIPITAL NERVE BLOCK FOR CLUSTER HEADACHE

Cluster headache has been described as the most painful condition that the patient has experienced. Great occipital nerve blockade is a short-term preventative treatment which commonly consists of the injection of a corticosteroid and local anesthetic into the suboccipital region. This analysis reviewed the efficacy of this intervention for patients with chronic cluster headaches.

A literature review was completed for studies including patients with cluster headaches, treated with occipital nerve blocks. Treatment effectiveness was defined as a change in frequency, severity, and duration of headaches.

After the literature review, the authors chose two, randomized, controlled trials (RCTs), and eight prospective and eight retrospective studies, which included a total of 595 patients. One RCT demonstrated a greater reduction in the mean number of attacks per day in the treatment group as compared with a control group over the 15 days after the first of the three injections. Both RCTs showed a statistically significant reduction in attack frequency over short time frames. The proportion of participants who responded in these studies ranged from 46.7% to 100%.

**Conclusion:** This literature review of studies of patients with cluster headaches concluded that a greater occipital nerve blockade is safe and effective for the prevention of cluster headaches.

Gordon, A., et al. Effectiveness and Safety Profile of Greater Occipital Nerve Blockade in Cluster Headache: A Systematic Review. *J Neurol Neurosurg Psychiatry.* 2023 Mar 22: jnnp-2023-331066. doi: 10.1136/jnnp-2023-331066. Online ahead of print.

### IMPACT OF COVID-19 IN PATIENTS WITH CHRONIC PAIN

Recent studies have described direct and indirect effects of COVID-19 in patients with pain. Some have suggested a disproportionate impact

of the pandemic on specific subgroups of individuals. This study described the trajectory of patients with chronic pain who sought treatment during the first two years of the pandemic.

This 26-month, observational, cross-sectional, retrospective, cohort study was completed at Stanford University's pain management center. Consecutive patient surveys, collected during the initial and follow-up visits, were included. A set of measures was used to assess social psychological aspects of the COVID-19 pandemic, including six primary outcomes of perceived threat of the COVID-19 virus, exposure to news about the pandemic, proximity to others afflicted by COVID-19, financial effects of COVID-19, resources, and psychological impacts. The subjects rated pain on a numeric rating scale (NRS), as well as secondary outcomes of pain intensity, pain catastrophizing, and PROMIS-pain interference, sleep, anxiety, anger, and depression scores.

The 1,270 patients who met inclusion criteria were included in the analysis. Over two years of follow up, significant improvements were noted in pain intensity ( $p < 0.001$ ) pain catastrophizing ( $p < 0.001$ ) and pain interference ( $p < 0.001$ ). Improvements were also noted in sleep disturbance ( $p < 0.001$ ), anxiety ( $p = 0.001$ ), anger ( $p < 0.001$ ), and depression ( $p = .016$ ).

**Conclusion:** This study of patients seen in a pain clinic found, that pain and pain related outcomes seemed to improve during the course of the COVID-19 pandemic

Ziadni, M., et al. A Longitudinal Investigation of the Impact of COVID-19 on Patients with Chronic Pain. *J Pain*. 2023, October; 24(10): 1830-1842.

### NATIONAL INSTITUTES OF HEALTH AND ABLEIST LANGUAGE

The National Institutes of Health (NIH) is a \$45 billion federal medical research agency. The current mission statement of the NIH is "to seek fundamental knowledge about the nature and behavior of living systems, and the application of that knowledge to enhance health, lengthen life and reduce illness and disability". In December 2022, a report of the advisory committee to the director working group on diversity, subgroup on individuals with disability, concluded that the current mission statement could be interpreted as perpetuating an ableist belief that disabled people are flawed

and need to be "fixed". The report noted that, on October 31st 1940, when Franklin Roosevelt dedicated the National Institute of health campus in Bethesda MD, he stood, holding the podium in order to perpetuate the image that his disability was less severe than it actually was. This ruse was perpetuated by the president himself who believed that the level of discrimination was such that the country would not accept a disabled president. Since that time a new social model now defines disability as resulting when societies erect physical, attitudinal and other barriers to participation in daily life. The 2011 World Health Organization (WHO) report on Disability declared that, "Disability is part of the human condition. Almost everyone will be temporarily or permanently impaired at some point in life". The proposed revised mission statement is "To seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to optimize health and prevent or reduce illness for all people."

**Conclusion:** This paper describes the current mission of the National Institute of health, and the proposed change in language designed to eliminate ableist language that serves to perpetuate the discrimination against those with disabilities.

lezzoni, L., et al. Revising NIH's Mission Statement to Remove Ableist Language. *JAMA*. 2023;330(20):1949-1950.

### PROTEIN Z IN ACUTE ISCHEMIC STROKE

Protein Z (PZ) /protein Z dependent protease inhibitor (PZI) is a newly discovered anticoagulant system which plays an important role in many diseases. This study assessed the effect of PZ/PZI on the risk of acute ischemic stroke.

This prospective cross-sectional study included consecutive patients hospitalized with an acute ischemic stroke, hospitalized between March 2013 and February 2016. A control group consisted of 85 non-stroke patients admitted to the physical examination center during the same timeframe. All underwent a medical evaluation for risk factors for stroke and were followed for severity and outcome of stroke. Blood levels were obtained for lipids, hs-CRP, platelets, prothrombin time, activated partial thromboplastin time D dimer PZ and PZI.

Compared with the control group, the stroke patients had greater levels

of hs-CRP ( $p < 0.001$ ) mean platelet volume ( $p = 0.003$ ), platelet distribution width ( $p = 0.01$ ), D-Dimer ( $p < 0.001$ ) and lower levels of PZ ( $p < 0.001$ ), and PZ/FII factor ( $p = 0.007$ ). A logistic stepwise regression found that that independent risk factors for acute ischemic stroke included PZ ( $p < 0.001$ ), D-dimer ( $p = 0.002$ ) and the hs-CRP ( $p < 0.001$ ).

**Conclusion:** This prospective cross-sectional study found plasma levels of protein Z to be an independent risk factor for acute ischemic stroke.

Pan, J., et al. Protein Z And Protein Z -Dependent Protease Inhibitor in Patients with Acute Ischemic Stroke: A Prospective Mechanistic Study. *J Stroke Cerebrovasc Dis*. 2023, December; 32(12): 107403.

### SUBJECTIVE AND OBJECTIVE COGNITION IN OLDER NATIONAL FOOTBALL LEAGUE PLAYERS

A cumulative exposure to repetitive head impacts may be associated with lower cognitive function among older former contact sport athletes. This study assessed both subjective and objective cognition in former National Football League (NFL) players to better understand their association.

Data were obtained from the Neurologic Function across the Lifespan: A Prospective, LONGitudinal, and Translational Study for Former National Football League Players (NFL-LONG). The subjects were former players who played at least one season in the NFL. The subjects completed a series of comprehensive health questionnaires including various self-report measures of health behavior, physical and social function. The participants reported all concussions sustained while playing football, even those that were not medically diagnosed. Participants 50 to 70 years of age were contacted to complete objective performance based cognitive testing. The Patient-Reported Outcome Measurement Information System (PROMIS) Cognitive Function Short Form version 2.0 was used as a validated measure of subjective cognitive function. Objective performance-based cognition was assessed using the Brief Test of Adult Cognition by Telephone (BTACT), comprised of six subtests that form two primary indices, including Episodic Memory and Executive Function.

Data were completed for 172 subjects with a mean age of 60.69 years. Greater concussion history was associated with lower subjective

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cognitive function but not performance-based cognition. Years of participation were not associated with measures of subjective or objective cognition. Subjective ratings of cognition were significantly associated with performance-based assessment with moderate effect sizes.

**Conclusion:** This study of former National Football League athletes found that subjective ratings of cognition were only moderately associated with cognitive performance, and that a greater concussion history was associated with decreased subjective but not objective cognitive performance.

Allen, A., et al. Subjective and Performance Based Cognition and Their Associations with Head Injury History and Older Former National Football League Players. **Med Sci Sports Exer.** 2022, December; 55 (12): 2170-2179.

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