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VAGUS NERVE STIMULATION PLUS REHABILITATION FOR STROKE

After an ischemic stroke, there are very few treatments that can effectively enhance upper extremity recovery. One proposed strategy involves cholinergic and monoaminergic modulation of motor cortex neurons, achieved through vagus nerve stimulation (VNS). This study assessed the effect of VNS on the recovery of upper extremity function.

This triple blinded, sham-controlled trial included adults between 22 and 80 years of age with ischemic strokes of at least nine months. All received rehabilitation sessions three times per week for six weeks. Six tasks were completed at each session with 30–50 repetitions for each task (>300 repetitions per session). Those randomized to the VNS group received stimulation with 0.8 mA, 100 μ s, 30 Hz stimulation pulses, lasting 0.5 s during these sessions. The control group received 0 mA impulses. The primary outcome variable was the change in Fugl-Meyer Upper Extremity (FMA-UE) score from baseline to study completion.

The change in FMA-UE was significantly greater in the VNS group than in the control group ($p=0.0014$). More patients in the VNS group than in the control group achieved a clinically meaningful response in the FMA-UE at 90 days ($p=0.0098$). Severe adverse events occurred in four percent of both groups.

Conclusion: This study of patients with moderate to severe upper extremity impairment after a chronic ischemic stroke found that vagus nerve stimulation, paired with conventional rehabilitation, could enhance upper extremity recovery.

Dawson, J., et al. Vagus Nerve Stimulation Paired with Rehabilitation for Upper Limb Motor Function after Ischaemic Stroke (VNS-REHAB): A Randomized, Blinded, Pivotal, Device

Trial. *Lancet*. 2021, April; 397 (10284): 1545-1553.

INTOLERABLE HIP PAIN FROM DELAYED SURGERY DURING COVID

A previous study demonstrated that, of those patients waiting for total hip arthroplasty (THA) or total knee arthroplasty (TKA), the percent who rate their quality of life to be “worse than death” was 19% and 12% respectively. As the United Kingdom (UK) ordered a cessation of “non-essential” surgeries due to COVID-19 in March 2020, this study investigated the effect of this order on the quality of life of these patients.

This multicenter, cross-sectional study was conducted across 10 orthopedic departments in the UK. Subjects were on a waiting list for either a THA or a TKA between August and September of 2020. The EuroQol-5 Dimension (EQ-5D) questionnaire was administered, with those patients scoring less than zero categorized as being in a state “worse than death”. Data from a previously published study were used as an unmatched control group and were thought to represent baseline data from 2004 to 2017.

The EuroQol-5 results found a quality of life worse than death in 35% of those waiting for a THA and 22.3% of those waiting for a TKA. This rate was close to twice that of the control group ($p=0.001$ and 0.001 , respectively).

Conclusion: This study found that the quality of life was rated as worse than death by approximately one third of patients waiting for total hip arthroplasty and one quarter of those waiting for a total knee arthroplasty.

Clement, N., et al. The Number of Patients “Worse Than Death” While Waiting for a Hip or Knee Arthroplasty has Nearly Doubled During the COVID-19 Pandemic. *Bone Joint J*.

2021, April: 103-B (4): 672-680.

TOPICAL AMITRIPTYLINE FOR PERIPHERAL NEUROPATHY

Amitriptyline is a tricyclic antidepressant with demonstrated efficacy for the treatment of neuropathic pain conditions. As several pilot studies have suggested that topical amitriptyline may be helpful in treating neuropathic pain, this study was designed to better understand the effectiveness of this treatment.

This three-part study included patients with chemotherapy-induced peripheral neuropathy (CIPN) and mice engaged in a nociceptive withdrawal test. The patients applied 1 g of 10% amitriptyline cream twice a day to each area of painful neuropathy. Neuropathic pain was assessed before and after one month of treatment using the Douleur Neuropathique en 4 (DN4) questionnaire. In the animal study, mice were tested for their nociceptive withdrawal threshold by sequentially increasing mechanical force until the mouse withdrew its paw from the device. This threshold was tested before and five minutes after the application of either a placebo cream or the study cream. In a third study, the mice were sacrificed for saphenous nerve analysis.

For the patients with CIPN, the mean baseline DN4 score was six out of ten, improving in one month to three out of ten ($p<0.001$). In the animal studies, mechanical withdrawal thresholds improved by 12%. *In-vivo* skin-saphenous nerve studies demonstrated that the amitriptyline inhibited the firing responses by 95.6%, 87.5% and 82.5% in C, A δ and A β fibers.

Conclusion: This study of peripheral neuropathy found topical amitriptyline useful for providing pain relief.

Genovois, A., et al. Analgesic Effects of Topical Amitriptyline in Patients with Chemotherapy-Induced

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Peripheral Neuropathy: Mechanistic Insights from Studies in Mice. **J Pain.** 2021, April; 22 (4): 440-453.

EFFECT OF GLUCOSE AND SODIUM CHLORIDE MOUTH RINSES ON NEUROMUSCULAR FATIGUE

Recent studies have shown that carbohydrate mouth rinse (CHO) can activate the insular and motor cortices, which subsequently excite the neuromuscular pathways, resulting in improved motor performance. As the activation of insular and motor cortices is not confined to carbohydrate (CHO) tastants alone, this study assessed the effect of glucose and sodium chloride (NaCl) mouth rinses on musculoskeletal performance.

This randomized, crossover study included 10 males who underwent trials of mouthwash including water only, six percent CHO or six percent NaCl. All underwent baseline testing of maximum aerobic capacity and cycling intensity. All cycled for 30 minutes at 70% VO₂ max followed by tests of MVC and sustained MVC (sMVC). The designated mouth rinse was given immediately before the cycling exercise, and at every 10-minute interval (10th, 20th and 30th minute) during the trial.

Greater post-cycling MVC loss occurred in the water group than the CHO group ($p = 0.0004$) and the NaCl group ($p = 0.0045$). The reductions produced by NaCl and CHO were similar. A two-way ANOVA revealed that water produced lower post-cycling sMVC peak force when compared to NaCl ($p = 0.04$) and CHO ($p = 0.004$).

Conclusion: This study demonstrates that salt (NaCl) mouth rinse shows comparable results to CHO mouth rinse in attenuating reductions of maximum voluntary contraction (MVC) and sustained MVC following a 30-minute cycling bout.

Khong, T., et al. Effect of Glucose and Sodium Chloride Mouth Rinses on Neuromuscular Fatigue: A Preliminary Study. **Euro J Sports Sci.** 2021; 21(2): 224-230.

WHOLE BODY VIBRATION COMBINED WITH BLOOD FLOW RESTRICTION

Blood flow restriction (BFR) exercise allows for gains in muscle hypertrophy with low load resistance

exercise. In addition, whole body vibration (WBV) has been shown to enhance training effects in certain training situations. This study assessed the effect of combining WBV with BFR during resistance training.

Subjects were 23 untrained adults, randomly assigned to a WBV group or a BFR + WBV group. All engaged in 10 sets of exercises with WBV for 20 minutes per day, three days per week, for eight weeks. The WBV + BFR group received the same WBV treatment, while adding BFR by compressing the proximal thigh, to arterial occlusion, using inflatable cuffs. The acute effect was assessed on the first training day. The subjects were assessed for rate of perceived exertion, muscle mass, maximum strength, muscular endurance, and changes in serum blood levels.

Muscle mass significantly increased over eight weeks in the BFR + WBV group, but not in the WBV group. Compared to baseline, follow up testing found that leg strength and muscle endurance significantly increased in both groups ($p < 0.05$), with greater increases in the combination group ($p < 0.05$). The one repetition max strength measure was increased by 11% in the combination group ($p < 0.05$) and by 4.5% in the WBV group, significantly better in the BFR + WBV group ($p < 0.05$).

Conclusion: Exposure to regular WBV + BFR training can increase thigh muscle mass, maximal strength, and muscle endurance to a greater extent than exposure to WBV training alone.

Cai, Z., et al. Effects of Whole-Body Vibration Training Combined with Blood Flow Restriction on Muscle Adaptation. **Euro J Sport Sci.** 2021. doi:10.1080/17461391.2020.1728389.

BLOOD FLOW RESTRICTION PLUS ELECTRICAL STIMULATION FOR MUSCLE ATROPHY

Blood flow restriction (BFR) has been found to amplify the treatment response to relatively light load exercise. This study investigated the effects of BFR combined with electrical muscle stimulation (EMS) to address muscular atrophy during periods of limb immobilization.

Subjects were 30, healthy adults with a mean age of 22 years, randomly allocated to a control group, a BFR group or a BFR+EMS group. All underwent a 14-day period of single leg muscle unloading through

the use of the knee brace and crutches. The control group underwent no intervention while the other groups received treatment twice per day, five days per week, for 20 treatment sessions. The BFR occurred for five minutes, three times per session, separated by five minutes of reperfusion. In the combination group, EMS was applied during the BFR sessions at an intensity to achieve knee extension torque equal to 15% of the maximum voluntary contraction. Muscle volume and strength were measured before and after intervention.

Compared with baseline measures, after two weeks of immobilization, whole thigh lean mass decreased in the control group by four percent ($p<0.001$) and in the BFR group by three percent ($p<0.001$), but not in the combined group. Vastus lateralis thickness decreased in the control group ($p=0.005$), trended toward a decrease in the BFR group ($p=0.07$) and increase in the BRF+EMS group ($p=0.07$). Also, knee extension MVC strength declined by 18% in the control group, 10% in the BFR group and 18% in the BFR+EMS group ($p=0.4$).

Conclusion: This study found that blood flow restriction combined with electrical stimulation may attenuate muscle mass loss during periods of immobilization.

Slysz, J., et al., Blood Flow Restriction Combined with Electrical Stimulation Attenuates Thigh Muscle Disuse Atrophy. *Med Sci Sports Exer.* 2021, May. 53 (5): 1033-1040.

AGNUSIDE FOR KNEE SYNOVITIS AND FIBROSIS

Studies of Knee Osteoarthritis (KOA) have shown that low grade inflammation in synovial tissue results in a state of local hypoxia, leading to HIF-1 α accumulation and NLRP3 inflammasome activation. As Agnuside (AGN) targets HIF-1 α / NLRP3, this animal study investigated the effect of AGN on the synovitis and fibrosis of KOA.

Subjects included 24 male rats, randomly assigned to groups of eight, including normal, KOA, and KOA +AGN. The KOA was induced by introducing 1mg monosodium iodoacetate (MIA) into both knees. Fourteen days after surgery, the KOA+AGN group began daily, oral doses of AGN (1 ml/100 g body weight/1 day) for 21 days. At 21 days, the rats were anesthetized, with

CRM serum and synovial tissues collected for analysis.

Using pimonidazole staining to assess hypoxia, synovial tissues of KOA showed aggravated hypoxia compared with the normal group. This was reduced in the KOA+AGN. Immunohistochemistry demonstrated that HIF-1 α -positive areas in the KOA group were upregulated compared with the normal group ($p<0.05$) and downregulated in the KOA+AGN compared with the KOA group ($p<0.05$). The KOA+AGN group also demonstrated decreases in levels of caspase-1, ASC and NLRP3, less inflammatory reaction, inflammasome downstream factors IL-1 β and IL-18, and fibrosis markers TGF- β , TIMP1, and VEGF.

Conclusion: This animal study demonstrates that the traditional Chinese medicine, agnuside, may attenuate synovitis and fibrosis of knee osteoarthritis by inhibiting HIF-1 α accumulation and NLRP3 inflammasome activation.

Zhang, L., et al. Agnuside Alleviates Synovitis and Fibrosis in Knee Osteoarthritis through the Inhibition of HIF-1 α and NLRP3 Inflammasome. *Mediators Inflamm.* 2021, March 16. doi.org/10.1155/2021/5534614.

ULTRASOUND FINDINGS IN RHEUMATOID ARTHRITIS-RELATED AND IDIOPATHIC CARPAL TUNNEL SYNDROME

While carpal tunnel syndrome (CTS) is associated with several rheumatologic disorders, idiopathic CTS is quite prevalent. Preliminary studies have suggested the potential for ultrasound (US) to assist with the diagnosis of CTS. This study compared the ultrasound findings of CTS patients with and without rheumatoid arthritis (RA).

Subjects were consecutive patients diagnosed with RA seen in the rheumatologic unit of Callo Urban Hospital in Ancona, Italy. Controls were consecutive patients diagnosed with idiopathic CTS. All underwent sonographic evaluation at the carpal tunnel level, evaluating median nerve swelling, measuring its cross-sectional area (CSA) at the carpal tunnel proximal inlet, finger flexor tendon tenosynovitis and radio-carpal joint synovitis. Patients were grouped as CTS + RA or CTS - RA.

Among 57 consecutive patients with RA, 26.3% were found to have CTS. The average CSA of the median nerve was higher in idiopathic CTS than in RA wrists with CTS

(17.7 mm² vs 10.6 mm², $p<0.01$), both of which were higher than those with CTS-RA (8.8 mm², $p<0.01$). A higher rate of inflammation of synovial structures (flexor tendons sheath and/or radio-carpal joint) was found in RA + CTS compared with RA- CTS ($p=0.04$) and idiopathic CTS ($p=0.02$).

Conclusion: This study found that the most characteristic sonographic features of carpal tunnel syndrome in patients with rheumatoid arthritis are those indicative of synovial tissue inflammation at the carpal tunnel level, while marked median nerve swelling is the dominant finding in idiopathic CTS.

Smerilli, G., et al. Ultrasound Assessment of Carpal Tunnel in Rheumatoid Arthritis and Idiopathic Carpal Tunnel Syndrome. *Clin Rheum.* 2021, March; 40(3): 1085-1092.

AGE OF DIABETES ONSET AND DEMENTIA

Diabetes is associated with a higher risk of cardiovascular morbidity and mortality, including the risk of dementia. This study was designed to understand the association between age at diabetes onset and incident dementia.

The Whitehall II study is an ongoing, British cohort study, established in 1985 through 1988 among 10,308 persons employed in London-based government departments. This cohort underwent seven clinical assessments between 1985 and 2016, at which blood samples were obtained for fasting blood sugar. Dementia cases were determined by linkage to three national registers: The National Health Service Database, the Mental Health Services Data Set, and the Office for National Statistics Mortality Register. Covariates included demographic information, health behaviors, and health-related variables.

Over the follow-up, of the 10,308 persons recruited in 1985, 1,710 (16.9%) developed diabetes. Of these, 153 (8.9%) were subsequently diagnosed with dementia. Of note, 48.3% of diabetes cases occurred after 70 years of age. At ages 60, 65 and 70 years, diabetes onset at an early age was strongly associated with dementia ($p<0.001$ for all). At age 70, compared to those without diabetes, those with diabetes onset more than 10 years earlier had an increased risk of dementia (Hazard

Ratio (HR) 2.12). With the same comparison, the HRs for dementia were 1.49 for diabetes onset six to ten years prior and 1.11 for those with diabetes onset five or fewer years prior ($p < 0.001$).

Conclusion: This longitudinal study found an association between the length of time since the diagnosis of diabetes and the risk of dementia.

Amidei, C., et al. Association between Age at Diabetes Onset and Subsequent Risk of Dementia. *JAMA*. 2021, April 27; 325(16): 1640-1649.

TOPICAL AMITRIPTYLINE FOR PERIPHERAL NEUROPATHY

Amitriptyline is a tricyclic antidepressant with demonstrated effectiveness for the treatment of pain associated with a range of neuropathic pain conditions. As several pilot studies have suggested that topical amitriptyline may be effective for treating neuropathic pain, this study was designed to better understand the effectiveness of this treatment.

This three-part study included patients with chemotherapy-induced peripheral neuropathy (CIPN), and mice engaged in a nociceptive withdrawal test. The patients applied 1 g of 10% amitriptyline cream twice a day to each area of painful neuropathy. Neuropathic pain was assessed before and after one month of treatment using the Douleur neuropathique en 4 (DN4,) questionnaire. In the animal study the mice were tested for a nociceptive withdrawal threshold using sequential increasing mechanical force until the mouse withdrew its paw from the device. This threshold was tested before and five minutes after the application of either a placebo cream or the study cream. In the third study, mice were sacrificed with the saphenous nerve removed for analysis.

For the patients with CIPN, 23 adults and two children ages 8-12 years completed the trial. At baseline, the patients had mean DN4 score of 6/10 improving in one month to 3/10 ($p < 0.001$). In the animal studies, mechanical withdrawal thresholds improved by 12%. *In vivo* skin-saphenous nerve studies demonstrated that the amitriptyline inhibited the firing responses of 95.6%, 87.5% and 82.5% in C, A δ and A β fibers. This response seemed dose dependent and was reversible within 30-35 minutes.

Conclusion: This study of chemotherapy-induced peripheral neuropathy found that topical amitriptyline could be useful for providing pain relief.

Genovois, A et al. Analgesic Effects of Topical Amitriptyline in Patients with Chemotherapy-Induced Peripheral Neuropathy: Mechanistic Insights from Studies in Mice. *J Pain*. 2021, April; 22 (4): 440–453.

POST-ACUTE SEQUELAE OF COVID-19

The acute clinical manifestations of COVID-19 are well-characterized, involving both pulmonary and extrapulmonary systemic manifestations. Beyond the acute setting, persistent, long lasting clinical manifestations have been noted, with these patients labeled “long haulers”. This study was designed to characterize and quantify the symptoms of this group.

The cohort included 23,435 adults receiving medical care in the Veterans Health Administration (VHA) who were diagnosed with COVID-19, did not require hospitalization, and survived the first 30 days after diagnosis. A control group comprised 4,990,835 VHA users without a COVID-19 diagnosis. These groups were compared for morbidity beyond the first 30 days.

Compared to controls, COVID-19 survivors had an increased risk of death within six months [Hazard Ratio (HR) 1.59]. In addition, an increased risk at six months was noted in the COVID-19 group for respiratory conditions (HR 28.51), respiratory failure (HR 3.37), neurocognitive disorders (HR 3.17), nervous system disorders (4.85) and headaches (4.10). For mental health, an increased risk was noted for sleep-wake disorders (HR 14.5), anxiety and stress related disorders (8.93). Also seen were increased risks of disorders of lipid metabolism (12.32), diabetes mellitus (8.23) and obesity (9.53). An excess burden was also found for cardiovascular conditions, including hypertension (15.18), cardiac dysrhythmias (8.4), circulatory signs and symptoms (6.65), esophageal disorders (6.9), gastrointestinal disorders (3.58), dysphagia (2.83) and abdominal pain (5.73).

Conclusion: This study found that, beyond the acute illness, those who survive the acute phase of COVID-19 experience a substantial burden of health loss, spanning

pulmonary and several extrapulmonary organ systems.

Al-Aly, Z., et al. High-Dimensional Characterization of Post-Acute Sequelae of Covid-19. *Nature*. 2021, April; doi: 10.1038/s41586-021-03553-9.

INTERVENTIONS FOR REDUCING SYMPTOMS OF DEPRESSION IN PEOPLE WITH DEMENTIA

Of the 15 million people in the world with a diagnosis of dementia, 32% experience symptoms of depression without a formal diagnosis of major depressive disorder. While medications have been the mainstay of treatment for depression, adverse effects of antidepressants inject caution when considering these interventions. This literature review compared the efficacy of drug and non-drug interventions for symptoms of depression in people with dementia.

Data were reviewed in multiple medical databases for publications through October of 2020. Of these studies, 235 reported outcomes for interventions that targeted symptoms of depression in patients with dementia and without a diagnosis of major depressive disorder.

Of these studies, 213 (25,177 people) in the primary network meta-analysis, cognitive stimulation, cognitive stimulation combined with cholinesterase inhibitor, exercise combined with social interaction and cognitive stimulation, massage and touch testing, multidisciplinary care, occupational therapy, and reminiscence therapy were more efficacious than usual care for reducing symptoms of depression.

The highest ranked interventions were cognitive stimulation combined with exercise and social interaction (98.3%, 88.3% to 100%), cognitive stimulation combined with a cholinesterase inhibitor (98.3%, 86.7% to 100%), and massage and touch therapy (95.0%, 86.7% to 100%). Drug approaches alone were not more efficacious than usual care.

Conclusion: This systematic review of studies of patients with depressive symptoms and dementia found that nondrug approaches were associated with a meaningful reduction in symptoms of depression, while drug approaches alone were not more beneficial than usual care.

Watt, J., et al. Comparative Efficacy of Interventions for Reducing Symptoms of Depression in People

with Dementia: Systematic Review and Network Meta-analysis. **BMJ.** 2021; 372: n532. Published 2021 March 24. doi:10.1136/bmj.n532.

PSILOCYBIN VERSUS ESCITALOPRAM FOR DEPRESSION

The main effects of psilocybin occur through serotonin 5-hydroxytryptamine type 2A (5-HT_{2A}) receptor agonism, which is part of a pathway implicated in depression. This study assessed the efficacy of psilocybin as a treatment for moderate to severe major depressive disorder.

Subjects were 18 to 80 years of age with a long-standing, moderate to severe major depressive disorder. Baseline testing included functional MRI and a battery of cognitive and affective processing tasks. After baseline testing, the subjects were randomized to receive two separate doses of 25 mg of psilocybin three weeks apart plus six weeks of daily placebo (psilocybin group) or two separate doses of 1 mg of psilocybin (negligible dose) three weeks apart plus six weeks of daily oral escitalopram (escitalopram group). The primary outcome measure was the change from baseline in 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) score at six weeks.

The mean changes in QIDS-SR-16 scores from baseline to week six were eight in the psilocybin group and six in the escitalopram group ($p=0.17$). A secondary analysis revealed a 50% or greater reduction in QIDS-SR-16 scores in 70% of the psilocybin group and 48% of the escitalopram group. Remission, defined as QIDS-SR-16 scores of zero to five, occurred in 57% of the psilocybin group and 20% of the escitalopram group.

Conclusion: This study of patients with a history of recalcitrant, moderate to severe, major depressive disorder found that psilocybin may be an effective intervention.

Carhart-Harris, R., et al. Trial of Psilocybin versus Escitalopram for Depression. **N Engl J Med.** 2021, April 15; 384 (15): 1402-1411.

BLOOD PRESSURE EFFECTS OF SODIUM REDUCTION

The association between dietary sodium intake and blood pressure (BP) has been studied extensively.

This literature review and meta-analysis was designed to better understand the effects of sodium intake reduction on systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Literature was reviewed for studies published through October of 2020. From these data, a dose-response meta-analysis was completed, assessing the relationship between changes in sodium intake and/or sodium excretion and SBP and DBP.

Data were pooled from 85 trials, with sodium intake ranging from 0.4 to 7.6 g per day. A linear regression analysis revealed that every 100 mmol/d reduction in urinary sodium excretion was associated with a lower mean SBP of 5.56 mm Hg and a lower mean DBP of 2.33 mm Hg. A 100 mmol/d decrease in sodium intake was associated with reductions in mean SBP and DBP of 7.79 mm Hg and 3.10 mm Hg respectively, among participants who had a baseline SBP of under 140 mm Hg. Among patients with a baseline SBP of 140 mm Hg or more, a similar reduction in sodium resulted in reductions of 6.06 mm Hg in SBP and 2.99 mm Hg in DBP, respectively. Overall, the pooled data were compatible with an approximately linear relationship between achieved sodium intake and mean SBP and DBP. The participants with hypertension had a much steeper dose response to sodium reductions for mean SBP and mean DBP over the entire range of achieved sodium excretion.

Conclusion: This meta-analysis confirms a positive and linear relationship between sodium intake and blood pressure.

Filippini, T., et al. Blood Pressure Effects of Sodium Reduction. **Circ.** 2021, April 20; 143(16): 1542-1567.

GENE LOCUS AND CHRONIC, WIDESPREAD MUSCULOSKELETAL PAIN

Chronic widespread pain (CWP) has an estimated global prevalence of 10.6%. While genetic factors are known to be shared by chronic pain conditions, data remain inconclusive regarding the effects of specific gene sites. This study of patients with CWP investigated the pathophysiological mechanisms of this condition.

A genome wide association study of patients with CWP was performed using the UK data bank, comprising

249,843 participants. CWP phenotypes were defined by combining self-reported diagnoses of all over body pain lasting for at least three months. The process identified three genome-wide significant loci implicating RNF123, ATP2C1 and COMT.

Of the loci implicated, only RNF123 was replicated, whereas ATP2C1 showed a suggestive association, and the COMT locus did not replicate. This RNF123 gene encodes E3 ubiquitin-protein ligase and plays a role in cell cycle progression, metabolism of proteins and innate immunity.

Conclusion: This large genome study using data from the UK data bank, identified a novel association between chronic, widespread pain and the RNF123 locus.

Rahman, S., et al. Genome-Wide Association Study Identifies RNF123 Locus as Associated with Chronic Widespread Musculoskeletal Pain. **Ann Rheumat Dis.** 2021, ;0-1: Doi:10.1136/Annrheumdis-2020-219624.

TEN-YEAR COURSE OF HIP OSTEOARTHRITIS

Hip osteoarthritis (OA) affects up to 25% of people older than 55 years. Despite its prevalence, little is known about the natural course of those with early signs of hip OA. This study describes the natural course of hip complaints among those presenting with hip and/or knee pain.

Data were obtained from the Cohort Hip and Cohort Knee (CHECK) study, a prospective, 10-year follow-up of first-time presenters with hip and/or knee pain. Data were obtained concerning physical function, education, body mass index and psychosocial factors. The Western Ontario and McMaster Osteoarthritis Index (WOMAC) was used to measure pain, stiffness, and physical function. Pain intensity was measured with the Numerical Rating Scale (NRS). Medical information, including hip x-rays, was recorded at baseline and for up to 10 years. Radiographic OA (ROA) was defined as a Kellgren and Lawrence (K/L) grade of two or greater.

Of the 1,002 participants, 588 reported hip pain at baseline, including 29% with only hip pain, and 71% with both hip and knee pain. At 10 years, 53% had ROA in at least one hip and 12% underwent hip replacement. Also at 10 years, only 51% still reported hip pain. The use

of any pain medication was found among 43% at baseline and 50% after 10 years. The number of individuals who were physically active remained stable over time.

Conclusion: This study of patients 45 to 65 years of age presenting with hip pain found that, at 10 years, 12% underwent hip replacement, with the remaining demonstrating stable symptoms over time.

van Berkel, A et al. Ten-Year Natural Course of Early Hip Osteoarthritis in Middle-Aged Persons with Hip Pain: A CHECK Study. *Ann Rheum Dis.* 2021, 80: 487-493.

URIC ACID AND PROGNOSIS IN ACUTE ISCHEMIC STROKE WITH REPERFUSION

As uric acid (UA) has an antioxidant effect, this study reviewed the relationship between changes in UA levels and outcome after acute ischemic stroke.

Subjects were consecutive patients diagnosed with acute, ischemic stroke, all of whom had been admitted to the Neurology Department of the West China Hospital between June 2018 and March 2020. Included were patients who were treated with reperfusion therapy, including intra-articular thrombolysis and/or endovascular thrombectomy. Uric acid was measured at baseline and at follow-up (median 92 hours) after revascularization. Absolute UA levels and changes in UA levels were compared with functional outcome (the modified Rankin Scale score (mRS)) at three months. A poor outcome was defined as an mRS score greater than two.

Patients were classified into tertiles according to baseline UA levels. Those in the highest two tertiles for UA levels had a significantly lower risk of poor outcome than those in the lowest tertile ($p=0.017$). A multivariate analysis found that the change in UA was positively related to poor outcome at three months, such that the greater the decrease in UA, the worse the outcome ($p=0.042$).

Conclusion: This study of patients with acute ischemic stroke found that low uric acid levels at admission and a greater decrease in uric acid during hospitalization were significantly related to poorer outcome at three months.

Wang, C., et al. Prognostic Significance of Uric Acid Change in Acute Ischemic Stroke Patients with Reperfusion Therapy. *Euro J Neurol.* 2021, April 28(4): 1218-1224.

EXTERNAL BIOFEEDBACK AND CHRONIC ANKLE INSTABILITY

Lateral ankle sprain is one of the more common musculoskeletal injuries, with a large portion of patients developing chronic ankle instability (CAI). This study assessed the effect of external visual and auditory feedback on the biomechanics of patients with CAI.

The subjects were 19 active adults with CAI and an average age of 23.9 years. All were assessed for single limb balance with the Accusway Optimized force platform. The subjects then performed four tests, either with or without biofeedback: Single limb balance, stepdown, lateral hop, and forward lunge. The performance was compared between conditions with and then without biofeedback. Visual biofeedback was provided by the crossline laser device, secured to the dorsum of the foot. Auditory biofeedback was given through a pressure sensor under the lateral foot set to alarm when pressure exceeded a preset threshold. The primary outcome was the location of center-of-pressure (COP) data points during balance tests with eyes open and eyes closed for each condition.

During eyes-open and eyes-closed static balance condition, the auditory-biofeedback condition produced a beneficial shift in COP location from the anterolateral to the posteromedial foot quadrant ($p=0.002$). The visual-biofeedback condition produced similar changes in COP location in the eyes-open trials. When performing the step down and forward lunge, participants were more responsive to auditory biofeedback, whereas during the lateral hop, they were more responsive to visual biofeedback.

Conclusion: This study involving patients with chronic ankle instability found that visual and auditory biofeedback improved static balance and functional-task biomechanics differently depending on the exercise.

Torp, D., et al. Biomechanical Response to External Biofeedback during Functional Tasks in Individuals with Chronic Ankle Instability. *J Athl Train.* 2021, March; 56 (3): 263–271.

INSULIN-LIKE GROWTH FACTOR, COGNITION AND SMALL VESSEL CEREBRAL DISEASE

The incidence and detection of cerebral small vessel disease (CSVD) have steadily increased over time. The main complication of CSVD is cognitive impairment. As insulin-like growth factor (IGF-1) plays a critical role in nerve growth and is associated with cognitive impairment, this study evaluated the association between serum IGF-1 levels and cognitive functioning among patients with CSVD.

Subjects were patients hospitalized with subcortical white matter hyperintensity and lacunar infarction. All underwent clinical evaluation and brain magnetic resonance imaging (MRI). Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), with additional variables including age, years of education, blood pressure, blood lipids, fasting blood glucose, fasting insulin, C-peptide, glycosylated hemoglobin, anti-human insulin antibodies and IGF-1.

Data were completed for 216 patients with CSVD, some with cognitive impairment (a CSVD-w group) and others without cognitive impairment (a CSVD-w/o group). Compared to the CSVD-w/o group, the CSVD-w group had significantly higher levels of fasting blood glucose, HbA1c, fasting insulin and anti-insulin antibodies ($p<0.05$), as well as lower IGF-1 and MoCA scores ($p<0.0001$). A controlled analysis revealed that IGF-1 levels were independently related to MoCA scores ($p<0.0001$).

Conclusion: This study of patients hospitalized with cerebral small vessel disease found that insulin-like growth factor levels were significantly related to cognitive scores, with lower levels among those with cognitive impairment.

Kang, J., et al. Positive Association between Serum Insulin-Like Growth Factor-1 and Cognition in Patients with Cerebral Small Vessel Disease. *J Stroke Cerebrovasc Dis.* 2021, July; 30(7): 105790.

ISOKINETIC STRENGTHENING FOR POST STROKE HEMIPLEGIA

At six months post-stroke, approximately 65% of individuals experience a reduced ability to perform daily living activities with the paretic arm. This study examined the efficacy of isokinetic upper extremity

strength training among patients with post-stroke hemiplegia.

Subjects were adults with post-stroke hemiplegia with Brunnstrom stage III motor recovery of the affected arm. Those participants were randomized to a control group or a treatment group, the latter performing isokinetic strength exercises for the wrist extensor and flexors three times per week for four weeks. All were assessed at baseline and follow-up with the Fugl-Meyer upper extremity (FM-UE) measure, the Stroke Impact Scale (SIS) and the Disabilities of the Arm Shoulder and Hand (DASH) scale. The control group received tailored, home-based strengthening exercises using blue exercise bands for wrist torques and peak isometric strength. The primary outcome variable was the change in isokinetic strength of the wrist and fingers.

Data were completed for 24 patients with a median post-stroke duration of 11 months. Changes in extensor peak torque at 60°/sn ($p=0.007$) and extensor peak isometric muscle strength ($p=0.007$) were higher in the isokinetic group ($n=12$) than in the control group ($n=12$). Significant improvements were found in the treatment group, but not in the control group, in the SIS measures of motion ($p=0.007$), ADLs/IADL ($p=0.024$), mobility ($p=0.017$), hand function ($p<0.001$) and DASH scores ($p=0.025$).

Conclusion: This study of patients with upper extremity paresis secondary to chronic stroke found that isokinetic exercises improved strength and function more than did conventional exercise.

Kerimov, K., et al. The Effects of Upper Extremity Isokinetic Strengthening in Post-Stroke Hemiplegia: A Randomized, Controlled Trial. **J Stroke Cerebrovasc Dis.** 2021, June; 30(6): 105729.

NEIGHBORHOOD BUILT ENVIRONMENT AND PHYSICAL ACTIVITY

According to the World Health Organization, long-term physical inactivity is the fourth largest risk factor for death globally. This study evaluated the effect of "built environment" on adult leisure time physical activity.

Sixteen communities were randomly selected from the Pingshan District of China. The Chinese Walkable Environment Scale for

urban community residents was used to measure the participants' neighborhood-built environment. A random selection was made of 10% of the families in each community, based on residential address. One member from each family was then randomly selected for evaluation. Levels of leisure time walking (LTW) and leisure time moderate to vigorous activity (LTMVPA) were measured using the leisure-time section of the International Physical Activity Questionnaire (IPAQ-long version). The frequency (days per week) and duration (minutes per day) of LTW and LTMVPA in the individuals past seven days were collected. This activity was compared with the scores on the Built Environment Scale.

Only 20.7% of participants engaged in active LTW and 17.8% active LTMVPA. After adjusting for other environmental variables, road conditions were associated with a higher likelihood of LTW (Odds Ratio (OR) 2.26) and LTMVPA (OR 2.26). A higher likelihood of active LTW was associated with positive neighborhood aesthetics (OR 1.35) and traffic conditions (OR 2.87).

Conclusion: This study found that residents who perceived their neighborhoods to have better aesthetics and traffic conditions were more likely to pursue active leisure time walking.

Yu, T., et al. Neighborhood Built Environment and Leisure Time Physical Activity: A Cross-Sectional Study in Southern China. **Eur J Sport Sci.** 2021, Feb; 21(2): 285-292.

SPOKEN WORD COMPREHENSION THERAPY FOR CHRONIC APHASIA

Randomized, controlled trials (RCTs) have provided unequivocal evidence that speech and language therapy can benefit people with aphasia across multiple language domains. This study investigated the efficacy of a self-led therapy application, *Listen In* to determine whether that therapy could effect changes in brain structure.

The self-care *Listen In* software was created to support self-led, high-dose therapy for persons with aphasia (PWA). Data were obtained from the Predicting Language Outcome and Recovery after Stroke database. Subjects with chronic strokes were randomized to receive 80 minutes per day of either standard care or *Listen In* care for 12 weeks.

The first co-primary outcome was spoken language comprehension on subtests of the Comprehensive Aphasia Test (CAT). The second co-primary assessment was the comprehension of trained and untrained spoken words using the Auditory Comprehension Test (ACT). Structural magnetic resonance imaging scans were obtained at baseline, during the period of testing, and at follow up.

Compared to the standard care group, the ACT scores in the treatment group demonstrated 11% greater improvement in spoken words ($p<0.001$), with these improvements maintained at 24 weeks. There was no parallel improvement for untrained words measured in the CAT. The change in ACT was associated with the volume of pre-therapy right hemisphere white matter and post-therapy grey matter tissue density changes in the bilateral temporal lobes.

Conclusion: This study of patients with chronic stroke and aphasia found that patients could improve their spoken word comprehension many years after the stroke.

Fleming, V., et al. Efficacy of Spoken Word Comprehension Therapy in Patients with Chronic Aphasia: A Crossover, Randomized, Controlled Trial with Structural Imaging. **J Neurol Neurosurg Psychiatry.** 2021, April; 92 (4): 418-424.

INTRAVENOUS ALTEPLASE AND POST-STROKE DEPRESSION

Post-stroke depression is a frequent complication of acute stroke, resulting in impaired recovery. This study assessed the effect of intravenous thrombolysis with alteplase on post-stroke depression (PSD), three months after an acute ischemic stroke.

The WAKE-UP trial was a multicenter, randomized, double-blind, placebo-controlled, clinical trial of MRI-based intravenous thrombolysis in patients with unknown onset stroke. This post hoc analysis included patients in whom a composite endpoint of PSD was defined as a Beck Depression Inventory ≥ 10 , medication with an antidepressant, or depression recorded as an adverse event. All subjects for this study presented with an acute ischemic lesion visible on diffusion-weighted imaging and met the clinical inclusion and exclusion criteria for intravenous alteplase. The

(Continued from page 2)

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participants were randomized to receive either alteplase or placebo. Depressive symptoms at 90 days post-stroke were assessed using the Beck Depression Inventory (BDI), a 21-item scale querying depressive symptoms, with a four-point rating (zero to three) for each item based on the severity of that item and adding up to total scores of zero to 63.

Post-stroke depression was observed in 42.9% of those in the alteplase group and 53.7% of those in the placebo group ($p=0.022$). A full model analysis revealed that significant predictors of PSD at 90 days post-stroke included stroke lesion volume (OR 2.24; $p<0.001$), a history of depression (OR 6.54; $p=0.045$), medication with antidepressants (OR 6.10; $p=0.005$) and treatment with placebo (OR 1.7; $p=0.024$).

Conclusion: This post hoc analysis of the WAKE-UP trial demonstrated that treatment with intravenous alteplase is associated with lower rates of post-stroke depression at 90 days after the stroke.

Konigsberg, A., et al. Effect of Intravenous Alteplase on Post-Stroke Depression in the WAKE-UP Trial. *Euro J Neurol*. 2021;doi.org/10.1111/ene.14797.

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