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INFLAMMATORY MARKERS AND KNEE OSTEOARTHRITIS

Once thought to be a non-inflammatory disease, recent findings indicate that chronic, inflammatory processes may be a driver in the progression of osteoarthritis (OA). This study used a proteomic approach to better understand inflammatory processes evident in the serum of patients with knee OA.

Subjects were 127 patients with OA of the knee (KOA), scheduled for knee replacement. Those patients were evaluated with the Knee Injury and Osteoarthritis Outcome Score (KOOS) and serum labs to assess the relative levels of 92 inflammation-related proteins. The distributions of these proteins were compared between the patients and 39 matched controls.

Fifteen markers were significantly different when comparing KOA patients with healthy participants. A positive relationship was seen between clinical pain and fibroblast growth factor-21, (p=0.008) and the expression of Eukaryotic translation initiation factor 4E-binding protein 1 (p=0.008). A linear regression model revealed that intensity of pain was significantly related to interleukin-6 (p<0.001), notch-like epidermal growth factor-related receptor (p=0.05), macrophage colony-stimulating factor 1 (p=0.015), fibroblast growth factor-21(p=0.002) and tumor necrosis factor superfamily member 12 (p=0.001).

Conclusion: This study of patients with severe osteoarthritis of the knee, identified 10 cytokines with significantly lowered expression in the serum, and five cytokines with higher expression levels as compared to controls.

Giordano, R., et al. Serum Inflammatory Markers in Patients with Knee Osteoarthritis: A Proteomic Approach. **Clin J Pain.** 2020, April; 36(4): 229-237.

METHYLPHENIDATE AND MILD COGNITIVE IMPAIRMENT

After a traumatic brain injury (TBI), individuals struggle with cognitive impairments, particularly impairment of executive function. As executive function can be manipulated by agents with an affinity for the dopaminergic or noradrenergic system, this study of patients with mild cognitive impairment after a TBI assessed the effect of methylphenidate on executive function.

Subjects were adults up to 35 years of age seen between October of 2015 and December of 2016 at Sultan Qaboos University Hospital and Khoula Hospital for evaluation and treatment of a TBI. All were tested with the Arabic version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQODE). Those with scores at level II (minor deterioration) were eligible for inclusion in the study. Executive function was tested using the Trail Making Test (TMT), the Wisconsin Sorting Test (WST) and the Tower of London (TOL) test. In addition, all were tested for verbal fluency, and screened for anxiety and depression symptoms with the Hospital Anxiety and Depression Scale (HADS). The subjects were tested at baseline, at the maximum dose of methylphenidate (10mg per day) and after methylphenidate withdrawal.

On measures of executive function, Digit Span scores increased with methylphenidate and decreased with withdrawal (p<0.001 for both comparisons). Treatment with methylphenidate also improved verbal fluency, which deteriorated after methylphenidate withdrawal (p<0.001 and p=0.008, respectively). Depression improved with methylphenidate (p=0.033), but did not deteriorate after withdrawal (p=0.150). Methylphenidate had no effect on anxiety.

Conclusion: This prospective, open label study of patients with mild cognitive impairment secondary to traumatic brain injury found that treatment with methylphenidate can improve executive function.

Al-Adawi, S., et al. Methylphenidate Improves Executive Functions in Patients with Traumatic Brain Injuries: A Feasibility Trial via the Idiographic Approach. **BMC Neurol.** 2020, March 19; 20(1): 103.

SELF-REPORTED FATIGUE AND INCIDENT STROKE

Fatigue is a common complaint, featured in 25% of patients seen in general practice consultations. Studies have shown that a complaint of fatigue is associated with an increase in all-cause cardiovascular mortality. This study examined the prospective relationship between self-reported, general fatigue and incident stroke.

This prospective, cohort study included adults, 39 to 79 years of age, each with no history of stroke or transient ischemic attack. All subjects completed a Short Form-36 questionnaire, vitality domain, (SF36-V) to evaluate self-reported fatigue. Incident strokes were recorded from death certificates and hospital records. Covariates commonly associated with fatigue and stroke were assessed at baseline. Non-fasting blood samples were collected, including cholesterol, thyroid stimulating hormone, and hemoglobin. The Health and Lifestyle questionnaire was administered at baseline, and included questions concerning demographic information, health behaviors and past medical history.

A total of 15,654 participants were included in the analysis. Within these, 1,509 cases of incident stroke were recorded. Fatigue was associated with an excess risk of stroke throughout the follow-up period. The fully adjusted model revealed that the hazard ratio for incident stroke was 1.49 among those who reported the greatest level of fatigue, as compared to those with the lowest level of fatigue (p<0.001). The presence of

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(Continued on page 8)

anemia, depression, thyroid dysfunction, chronic obstructive pulmonary disease and cancer did not attenuate the effect of fatigue.

Conclusion: This population based, prospective, cohort study demonstrates an independent association between self-reported fatigue and the risk of incident stroke.

Barlas, G., et al. Self-Reported Fatigue Predicts Incident Stroke in a General Population: EPIC-Norfolk Prospective, Population-Based Study. **Stroke.** 2020, April; 51(4): 1077-1094.

POLYMYALGIA RHEUMATICA AND ENDOTHELIAL FUNCTION

Polymyalgia rheumatica (PMR) is a chronic inflammatory disease, characterized by shoulder and hip pain and an elevation of acute phase reactants. As this is a chronic inflammatory disease, this study evaluated the endothelial function and atherosclerotic burden among newly diagnosed, steroid-naïve patients with PMR.

Subjects were 16, consecutive, adult patients with newly diagnosed PMR. All underwent clinical and vascular evaluations at baseline and up to 12 months' follow-up. Baseline evaluations included routine laboratory tests. All were treated with prednisone at 0.2 mg/kg per day for the first month, followed by a 50% tapering of the dose every four weeks until the lowest therapeutic dose was achieved. Clinical remission was defined as the lack of girdle pain and laboratory remission as levels of ESR 25 mm/h or less and CRP of 5 mg/L or less. Blood vessels were evaluated by ultrasound, with endothelial function assessed using the flow mediated dilatation (FMD) technique.

At baseline, compared to controls, patients with PMR had higher values of both ESR ($p<0.001$) and CRP ($p<0.001$). At baseline, the mean FMD of the PMR patients was significantly lower than that of controls ($p<0.001$). A negative relationship was found between FMD values and both ESR ($p=0.019$) and CRP values ($p=0.001$). At one-year follow-up, symptoms had improved, with 15 achieving clinical remission and 13 achieving laboratory remission, with complete normalization of acute-phase reactants (ESR< 25 mm/h, CRP< 5 mg/L). No significant differences in FMD values were seen between patients achieving remission and those with persistent, active disease.

Conclusion: This study of patients newly diagnosed with polymyalgia rheumatica found that, compared to that of controls, endothelial function was impaired, with this impairment persisting after clinical remission.

Santoro, L., et al. Subclinical Atherosclerosis and Endothelial Dysfunction in Patients with Polymyalgia Rheumatica: A Pilot Study. **Scand J Rheumatol.** 2020; 49 (1): 68-74.

STRESS RELATED DISORDERS AND SUBSEQUENT NEURODEGENERATIVE DISEASES

Epidemiologic studies have suggested that stress exposure is associated with the risk of dementia. However, less is known about the association between stress related disorders and other neurodegenerative diseases. This study was designed to better understand the association between a range of stress related disorders and the subsequent risk of neurodegenerative diseases.

Using the Swedish National Patient Register (NPR) the authors identified all Swedish born individuals diagnosed with a stress-related disorder between January 1, 1987, and December 31, 2008. These disorders were divided into post-traumatic stress disorder (PTSD), acute distress reaction, adjustment disorder, and other stress reactions. Each of these individuals was matched with 10 controls who were free of stress-related disorders. Neurodegenerative diseases were categorized according to their potential origin, including primary and vascular causes.

Data were collected for 61,748 exposed individuals and 595,335 matched, non-exposed individuals. During follow up, 3,822 individuals were identified with incident neurodegenerative diseases, resulting in a crude incidence rate of 1.50/1000 person-years for exposed individuals and 0.82/1000 person-years for unexposed individuals (Hazard Ratio (HR) 1.57). This risk was greater for vascular neurogenerative disease (HR 1.80) than for primary neurodegenerative diseases (HR 1.31).

Conclusion: This study found that stress-related disorders are

associated with an increased risk of neurodegenerative diseases.

Song, H., et al. Association of Stress Related Disorders with Subsequent Neurodegenerative Diseases. **JAMA Neurol**. 2020 Mar 9. doi: 10.1001/jamaneurol.2020.0117.

NEUROMUSCULAR ELECTRICAL STIMULATION PRESERVES LEG LEAN MASS IN GERIATRIC PATIENTS

Age-related loss of muscle mass is associated with poor mobility, loss of independence and increased mortality. The number of nonconsecutive days spent in the hospital during a year is associated with loss of muscle mass and strength in the elderly. This study investigated the effect of neuromuscular electrical stimulation (E-stim) on changes in muscle mass and muscle fiber size in hospitalized, geriatric patients.

Patients admitted to a geriatric ward, 65 years or older, were assessed at admission and discharge with muscle scans, muscle biopsies and tests of muscle function. The intervention consisted of a daily, 30-minute session of E-stim applied to the vastus lateralis and vastus medialis muscles of one leg (E-stim). The contralateral leg served as a control (CON). Stimulation was increased as tolerated, to a peak of 89 mA at the end of the last session. Lean mass was assessed with whole-body, dual-energy, x-ray absorptiometry. Muscle thickness was measured by ultrasound, with immunohistochemistry used to assess muscle fiber cross-sectional area, fiber type and satellite cell (SC) proliferation.

Thirteen patients completed the study. Lean muscle mass declined in the CON leg by 2.8% and in the E-stim leg by 0.5% ($p<0.05$). No significant differences were noted between the legs on tests of muscle power, torque or muscle fiber size. Compared with the CON leg, stimulation resulted in a down regulation of several atrophy signaling pathways and an upregulation of connective tissue and cellular remodeling processes in the E-stim leg.

Conclusion: This study of hospitalized geriatric patients found that 30 minutes of electrical stimulation to the lower extremity helps preserve lean muscle mass.

Anders, K., et al. Neuromuscular Electrical Stimulation Preserves Leg Lean Mass in Geriatric Patients. **Med Sci Sports Exerc**. 2020, April; 52(4): 773-784.

VITAMIN D AND MULTIPLE SCLEROSIS

Vitamin D, a potent immunomodulator, has been associated with the pathogenesis of multiple sclerosis (MS). This study assessed the relationship between serum 25(OH)D levels and MS related disability.

The baseline cohort comprised 51 patients with relapsing-remitting multiple sclerosis (RRMS), and two patients with clinically isolated syndrome (CIS) with a mean age of 43 years, a mean disease duration of nine years and Expanded Disability Status Scores of below 6.5. The participants were assessed for serum 25(OH)D, with cutoffs chosen as those proposed by the American Institute of Medicine for bone health. Those with serum 25(OH)D levels of below 30 ng/ml (low) were compared to those whose serum levels were higher (high). The Expanded Disability Status Score (EDSS) scores and MRI findings were compared between groups.

The 53 patients' mean age was 43 years, with 69.8% female and a median serum 25(OH)D of 18 ng/ml. An inverse association was found between EDSS scores and 25(OH)D levels, after adjusting for age, gender and disease duration($p<0.001$). The median T2 lesion counts were 25 in the high vitamin D group and 60 in the low vitamin D group ($p<0.001$).

Conclusion: This study of patients with relapsing-remitting multiple sclerosis/CIS, found an inverse relationship between vitamin D levels and measures of disability.

Baker-Koduah, P., et al. Vitamin D and Disease Severity in Multiple Sclerosis-Baseline Data from the Randomized, Controlled Trial (EVIDIMS). **Frontiers Neurol.** 2020, February doi: 10.3389/fneur.2020.00129.

DIETARY PROTEIN INTAKE AND MORTALITY

Several short-term, randomized, clinical trials have suggested that the consumption of high-protein diets may favor weight management and improve lipid profiles and glycemic regulation. However, several prospective studies have reported that long-term high protein intake may be associated with a higher risk of type II diabetes and cardiovascular disease. This study investigated the associations of total protein intake and protein from different food sources with all-cause and cause-specific mortality.

Data were obtained from the Rotterdam study, a prospective, cohort study of adults 45 years and older, with the first cohort initiated in 1989. Data were analyzed for 7,786 individuals for whom dietary data and long-term follow-up data were available. Diet was assessed with a semi-quantitative food questionnaire (FFQ). Dietary protein and other macronutrients were expressed as a percentage of total energy consumption. For those who died during the study, cause-specific mortality was recorded. In addition, a systematic literature review and meta-analysis was conducted.

During a median follow-up of 13 years, 3,589 deaths were recorded. Higher total protein intake was associated with a higher risk of all-cause mortality ($p=0.06$), cardiovascular disease mortality ($p=0.06$) and non-stroke, cardiovascular disease mortality ($p=0.04$). Compared to the lowest quartile of protein intake, those in the highest quartile had a greater risk of all-cause mortality (HR 1.12). These associations were mainly explained by animal protein intake and CVD mortality (HR=1.60). Total plant protein intake was not associated with all-cause or cause-specific mortality. The meta-analysis of 11, prospective, cohort studies also found that higher protein intake was associated with higher all-cause mortality, mainly due to an association between animal protein and CVD mortality. Higher plant protein intake was associated with lower all-cause and CVD mortality (HR=0.87).

Conclusion: This prospective study, followed by a literature review and meta-analysis, found that protein intake is positively associated with all-cause mortality, mainly due to an association between animal protein mortality and cardiovascular disease.

Chen, Z., et al. Dietary Protein Intake and All-Cause and Cause-Specific Mortality: Results from the Rotterdam Study and a Meta-analysis of Prospective, Cohort Studies. **Eur J Epidemiol**. 2020, https://doi.org/10.1007/s10654-020-00607-6.

PATELLOFEMORAL PAIN SYNDROME AND X TAPING

Patients with patellofemoral pain syndrome (PFPS) often report an escalation of symptoms when moving up or down stairs, running, jumping or squatting. Some have reported that knee pain reduction with posterior X taping may be in part due to decreased internal tibiofemoral rotation. This study investigated the effects of posterior X taping on the pain and function of patients with PFPS.

Participants were 16 individuals diagnosed with PFPS, all with a visual analog pain scale score of at least 30 out of 100. Non-elastic tape, 3.75 cm wide, was applied to the tested knee in the sitting position, with the knee flexed 20°. A strip of tape was applied, starting from the proximal-lateral thigh around posterior knee to the distal-medial tibia for reduction of femoral medial rotation and tibial lateral rotation. A second strip started from the proximal -medial thigh around posterior knee to the distal-lateral tibia for symmetry or preventing knee hyperextension. The strips of tape formed an "X" around the posterior knee. A 3-D motion analysis system was used to measure kinematics of the lower extremity during a forward step-down (FSD) performance test, with and without tape.

Sixteen patients participated in the study, with a mean age of 38 years. The FSD test scores were significantly more improved in the taping condition as compared to the no tape condition (p=0.002). Motion analysis failed to demonstrate changing kinematics of the hip, knee or ankle joints with taping.

Conclusion: This study of patients with patellofemoral pain found that posterior X taping with non -elastic tape improved pain and function during activity, but had no effect on tibiofemoral rotation.

Lim, E., et al. Effects of Posterior X Taping on Movement Quality and Knee Pain Intensity during Forward-Step-Down in Patients with Patellofemoral Pain Syndrome. **J Sports Sci Med.** 2020; 19: 224-230.

VITAMIN D AND AEROBIC PERFORMANCE IN COMBAT SPORTS

Vitamin D receptors are found in nearly all human nucleated cells. Nearly 15% of the world's population has a vitamin D deficiency. Supplementation with vitamin D has been shown to increase the force and power output of skeletal muscle. Little is known however about the effect of vitamin D_3 supplementation and aerobic performance. This study assessed whether supraphysiological doses of vitamin D_3 could improve aerobic performance in male combat sports athletes.

Subjects were 21 recreational combat sports athletes who trained at least twice per week. At baseline, serum was drawn to assess hematocrit and hemoglobin and vitamin D levels. Aerobic performance was assessed at baseline and after six weeks of placebo, and then after six weeks of vitamin D supplementation. Weekly, the subjects consumed three capsules of placebo, with 300 ml of Jersey full fat milk and provided a three-day food diary. After six weeks the participants were then assigned to weekly doses of 50,000 IUs (n=9), 80,000 IUs (n=9) or 110,000 IUs (n=9) of vitamin D_3, with 300 ml of Jersey full fat milk for six weeks. Participants were tested for upper body and lower body peak power and average power.

The hemoglobin and hematocrit were unchanged during the placebo period but rose five to eight percent during the intervention trial. There was a significant effect for time for hemoglobin and hematocrit, upper and lower body VO_{2peak} and upper body Wingate power ($p<0.01$). No additional benefit was found when increasing dose above 50,0000 IU vitamin D_3 per week.

Conclusion: This study of recreational combat sports participants found that supplementation with vitamin D improved aerobic performance with a concurrent improvement in hemoglobin concentrations and hematocrit.

Marley, A., et al. Weekly Vitamin D3 Supplementation Improves Aerobic Performance in Combat Sports Athletes. **Europ J Sport Sci.** 2020, March;18:1-19.

MESENCHYMAL STROMAL CELLS FOR KNEE ARTHRITIS

Autologous stromal vascular fraction (SVF) cells consist of a heterogeneous concentration of nucleated stromal and vascular cells that do not contain adipocytes, with a low concentration of leukocytes and extracellular matrix. This study investigated the efficacy and safety of intra-articular, autologous SVF injections, compared with placebo, for the treatment of osteoarthritis (OA) of the knee.

Subjects were 40 to 75 years of age, all with OA of the knee, who also had Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale scores of between six and 16 in one knee, and six or less in the contralateral knee. The patients were randomized in a 1:1:1 fashion to receive high-dose (3.0×10^7 SVC cells), low-dose (1.5×10^7 SVC cells) or placebo knee injections. All injections were performed in a blinded manner using a syringe with a total volume of 3 to 4 mL. The primary efficacy outcome was the percentage change from baseline in the WOMAC scale. MRIs were obtained before treatment and 12 months after treatment.

Of the 39 patients enrolled, 37 completed the six-month evaluation. The median percentage changes in WOMAC scores for the high-dose, low-dose and placebo groups were 83.9%, 51.5% and 25.0%, respectively. Sixty-two percent of the patients in the treatment groups (high and low doses) had a response greater than the Minimally Clinically Important Difference (MCID), as compared to only 38% of the participants in the placebo group. At one year, the high- and low-dose groups continued to display a significantly greater percentage improvement in WOMAC scores, as compared with the placebo group (high dose, p=0.006; low dose, p=0.009). The MRI scans revealed no visibly quantifiable changes in knee cartilage thickness, or any evidence of differences between groups in disease progression.

Conclusion: This randomized, controlled trial including patients with osteoarthritis of the knee found that autologous stromal vascular fraction cells, injected into the knee, can significantly improve pain and function, as compared with placebo.

Garza, J., et al. Clinical Efficacy of Intra-Articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis: A Double-Blinded, Prospective, Randomized, Controlled, Clinical Trial. **Am J Sport Med.** 2020, March; 48 (3): 588-598.

SURGERY VERSUS CONSERVATIVE CARE FOR PERSISTENT SCIATICA

Sciatica, caused by acute herniation of a lumbar disc, is

expected to improve with conservative care. This study compared the efficacy of lumbar discectomy to that of nonsurgical care in patients with sciatica lasting four to twelve months.

This prospective, randomized, controlled trial included patients, 18 to 60 years of age, each with a history of unilateral lumbar radiculopathy lasting four to twelve months. All had findings on magnetic resonance imaging of disc herniation compressing the corresponding nerve root. The 128 patients were randomized to surgical or nonsurgical treatment. Nonsurgical care included education about day-to-day functioning, activity and exercise, use of oral analgesics, and physiotherapy as provided at the discretion of the physiotherapist. The surgical group underwent microdiscectomy. Outcomes were assessed at baseline and up to one year after enrollment. The primary outcome measure was the leg pain intensity score on the visual analog scale (VAS). Secondary outcomes included scores on the Oswestry Disability Index, 36 Item-Short Form General Health Survey (SF-36), Physical and Mental components.

At six months, the mean VAS scores for leg pain intensity were 2.8 in the surgical group and 5.2 in the nonsurgical group ($p<0.001$). At one year, the mean VAS for leg pain intensity was 2.6 in the surgical group and 4.7 in the nonsurgical group ($p<0.001$).

Conclusion: This study of patients with chronic sciatica lasting for up to 12 months found surgical intervention to be superior to conservative intervention for pain reduction.

Bailey, C., et al. Surgery versus Conservative Care for Persistent Sciatica Lasting Four to 12 Months. **N Engl J Med.** 2020, March 19; 382: 1093-1102.

ELECTROCARDIOGRAPH ABNORMALITIES AND STROKE RISK

Isolated, nonspecific, ST-segment and T-wave abnormalities (NSSTTAs) are common findings on the resting electrocardiograph in asymptomatic individuals. This study evaluated the significance of NSSTTAs on incident ischemic stroke, independent of known risk factors.

This nationwide stroke study included randomly selected community dwelling individuals 45 years of age or older. All subjects participated in a 45-minute interview used to collect date concerning demographics, socioeconomic status, stroke risk factors, and medical history. The interview was followed by a home visit to collect blood and urine specimens, EKG results, blood pressure, waist circumference, height and weight. At six-month intervals, the participants were contacted by phone, followed by an in-home physical examination, and were asked about stroke symptoms, hospitalizations, and health status. The outcomes of those with baseline NSSTTAs were compared to those without NSSTTAs at baseline.

Of the 14,077 participants 3,111 had isolated NSSTTAs. During a median follow-up of 9.6 years, ischemic strokes were found in 3.4% of those with NSSTTAs and in 2.4% of those without NSSTAs ($p<0.0001$). After adjusting for risk factors, the finding of NSSTTAs was associated with a 27% increased risk of stroke.

Conclusion: This study of community dwelling adults found that those with isolated NSSTTAs on resting echocardiograph had a significantly higher risk of incident ischemic stroke, independent of traditional risk factors.

Sawano, M., et al. Electrocardiographic ST-T Abnormalities are Associated with Stroke Risk in the REGARDS Study. **Stroke.** 2020, April; 51(4); 51: 1100-1106.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND ISCHEMIC STROKE

While several observational studies have found associations between selective serotonin reuptake inhibitors (SSRIs) and an increased risk for intracerebral hemorrhage (ICH), no consensus exists. This study further explored the risk of ICH and outcomes among patients with SSRI use.

This multi-center, prospective, observational, case control study included 3,000 adult patients with a primary ICH event, all matched to ICH-free controls. Medication use, including antidepressants, was recorded for all patients. The use was categorized as previous (prior to ICH only), new post-ICH (at discharge or three months, but not pre-ICH), continuous (before and after ICH) and no use (neither pre- nor post-ICH use). Covariates were also collected. Neurological outcome was measured with a modified Rankin Scale (mRS) score for before ICH, at discharge and at three-month follow-up. Any diagnosis of depression during hospitalization was recorded.

No significant relationships were found between pre-ICH use of an SSRI continued SSRI use and unfavorable outcome at three months. However, an adjusted analysis revealed that new SSRI use post-ICH was associated with an unfavorable outcome ($mRS\geq3$) at three months after ICH ($p=0.015$). In a subset analysis, while not true for white or black patients, among Hispanics, SSRI use before an ICH was associated with a reduced risk of ICH ($p=0.014$).

Conclusions: This large, multi-ethnic, prospective, case-control study found an increased risk of intracranial hemorrhage among patients who initiated the use of selective serotonin reuptake inhibitors after an ICH, with no ill effects among those taking these medications before their stroke. However, use of these medications was not associated with an increased risk of first ICH; and in Hispanics this resulted in a reduced risk of ICH.

Liu, L., et al. Selective Serotonin Reuptake Inhibitors and Intracerebral Hemorrhage Risk and Outcome. **Stroke.** 2020, April; 51 (4): 1135-1141.

BOTULINUM TOXIN TYPE A IMPROVES GOAL ATTAINMENT IN ADULTS WITH POSTSTROKE LOWER LIMB SPASTICITY

Botulinum toxin is a proven, effective, and well-tolerated treatment for adults who suffer from spasticity as a result of upper motor neuron pathology. This study evaluated the functional gains of patients with spasticity treated with botulinum toxin A (BoNT-A).

This prospective, multi-center observational study included 100 patients with post-stroke lower limb spasticity. After baseline assessments, the patients received lower extremity injections with BoNT-A based on standard of care guidelines. Assessments at baseline and follow up included the Goal Attainment Scale (GAS), as the primary outcome measure, with additional assessments including the Modified Ashworth Scale, the Demeurisse Motricity Index, the 10-meter walk test, and the Disability

Assessment Scale (DAS). One primary treatment goal and up to two secondary goals were agreed upon by the patient/caregivers. The achievement of goals was determined at visit two.

The most common primary goal of treatment was improved mobility (57.5%), followed by improved positioning (18.1%). At follow-up, the GAS goal was achieved in 88.4%. In the subgroup of patients who had better mobility as their primary goal, 87.0% reported that this had been achieved. For those with better positioning as the primary goal, this was achieved by 100%. Factors that were predictive of not obtaining the GAS included greater time since stroke onset (p=0.038) and absence of a stiff knee spasticity pattern (p=0.036).

Conclusion: This study of patients with spasticity due to stroke found that treatment with botulinum toxin resulted in significant improvement in mobility and positioning.

de Munain, L., et al. Botulinum Toxin Type A Improves Function According to Goal Attainment in Adults with Post -Stroke Lower Limb Spasticity in Real Life Practice. **Euro Neurol.** 2019; 82: 1-8.

NERINETIDE FOR THE TREATMENT OF ACUTE ISCHAEMIC STROKE

The post-synaptic density protein 95 (PSD-95) is an abundant synaptic scaffolding protein that interacts with neurotoxic signaling proteins. Nerinetide, an eicosapeptide, was designed to perturb those PSD-95 protein-protein interactions that can lead to cytotoxic death in acute ischemia. Nerinetide can penetrate the blood brain barrier and has been shown to reduce stroke damage in primates. This study assessed the effect of nerinetide in patients with acute, ischaemic stroke.

This multicenter, randomized, double-blind, placebo-controlled study recruited patients with acute, ischaemic stroke who were scheduled to undergo endovascular therapy (EVT). Eligible subjects had National Institute of Health Stroke Scale (NIHSS) scores of greater than five, with proximal intracranial artery occlusion and a small to medium ischaemic core. The participants received intravenous alteplase according to usual care, before or during EVT. The subjects received a single intravenous dose of nerinetide or oral placebo randomized independently of the other drugs in the trial. A good outcome was defined as a score of zero to two on the modified Rankin Scale (mRS).

Of the 1,105 patients in the study, alteplase was administered to 60.1% in the nerinetide group and 59.2% in the placebo group. Of those who did not receive alteplase, 59.3% who received nerinetide achieved a good outcome (mRS 0-2), as compared with 49.8% who received placebo (RR 1.18). The absolute risk reduction in mortality at 90 days was 7.5% among those who received nerinetide but who did not receive alteplase, compared to those who also received alteplase. By contrast, no protective effect of nerinetide was seen among those who received alteplase.

Conclusion: This study of patients with acute, ischaemic stroke found that nerinetide can significantly improve functional outcomes, an effect that seems to be inhibited by concurrent treatment with alteplase.

Hill, M., et al. Efficacy and Safety of Nerinetide for the Treatment of Acute Ischaemic Stroke (Escape-NA1): A Multicenter, Double-Blind, Randomized, Controlled Trial. **Lancet.** 2020, March; 395(10227):14 -20: 878-887.

MUSCULOSKELETAL DISORDERS AND HEMODIALYSIS PATIENTS

Hemodialysis-related arthropathy is a clinical, biological and radiological entity that encompasses the tunnel syndromes and articular, bone and vertebral abnormalities. The frequency and severity of these disorders increase with length of dialysis, especially in patients undergoing hemodialysis for 30 years. This study was designed to estimate the prevalence of musculoskeletal manifestations in patients undergoing hemodialysis.

This cross-sectional study included patients treated in the dialysis unit of one hospital in Beirut. The medical records and the patients themselves were queried concerning musculoskeletal symptoms.

Musculoskeletal symptoms were reported by 76.4%, with the most common including pain (44.9%) paresthesias (16.9%), joint swelling (12.4%) and cramps (15.9%). These symptoms corresponded to diagnoses of osteoarthritis (53.9%), mainly in the spine (32.6%), knee (18%) and shoulder (10.1%). Low energy fractures occurred in 27%, mostly in the hip (12.4%). Tendinopathy occurred in 22.5%, most frequently in the shoulder (8.8%). Carpal tunnel syndrome occurred in 18%.

Conclusion: This study of patients on hemodialysis found that 76.4% had musculoskeletal complaints, with the main diagnoses including osteoarthritis in 53.9% and fracture in 27%. The prevalence of musculoskeletal manifestations is high in the hemodialysis population and increases with dialysis vintage.

Hage, S., et al. Musculoskeletal Disorders in Hemodialysis Patients: Different Disease Clustering According to Age and Dialysis Vintage**. Clin Rheum.** 2020, February; 39(2): 533-539.

TOTAL HIP ARTHROPLASTY IN CEREBRAL PALSY

Among patients with cerebral palsy (CP), hip subluxation and dislocation can give rise to secondary osteoarthritis and degeneration of the femoral head. Many require surgical intervention to improve quality of life. For years, pelvic and proximal femoral osteotomies were performed, resulting in pain reduction, but with little improvement in function. Recently, total hip arthroplasty (THA) was introduced to reduce morbidity and to increase function. This systematic review was designed to better understand the efficacy of THA in this population.

A systematic review was completed of studies involving patients with CP who underwent THA. From that review, nine studies met the inclusion criteria and were summarized. All studies reported a significant reduction in pain after surgery. In addition, most patients reported a significant improvement in functional capacity and a reduction of burden for the primary caregivers. Postoperative complications were reported to be as high as 26% and included recurrent dislocations and trochanteric bursitis.

Conclusion: This literature review of patients with cerebral palsy undergoing total hip arthroplasty found that the majority of the studies reported significant pain relief and improved functional outcome after surgery.

Adams, C., Clinical and Functional Outcomes of Total Hip Arthroplasty in Patients with Cerebral Palsy: A Systematic Review. **J Ortho** 2020; 21; 19-24.

NON-IMMERSIVE VIRTUAL REALITY REHABILITATION FOR STROKE PATIENTS

Therapeutic interventions during stroke rehabilitation often involve a task-oriented approach. Virtual reality (VR) training can be used to create an applicable practice environment for such training. This study evaluated the effect of non-immersive VR training on the functional outcomes of patients with hemiparetic stroke.

This randomized, controlled trial included 36 patients with a primary stroke within six months of enrollment. Subjects were randomized to an intervention group who received non-immersive VR training using the RAPAEL smart glove or to a control group. Both groups underwent 24 sessions of 30 minutes each, three days per week for eight weeks. A control group played video games as a recreational activity. In the intervention group, an algorithm was applied to game-like exercises, proposing an optimally challenging task with the proper amount of difficulty. Outcome measures included the Box and Block Test (BBT), the Jebsen-Taylor Hand Function Test (JT), assessment of grip strength and the Wolf Motor Function Test (WMFT).

Compared with baseline measurements, both groups achieved significant improvement on all outcome measures. Compared to the control group, improvement in the intervention group was greater for the BBT ($p<0.001$), grip strength ($p<0.001$) and the WMFT ($p=0.032$).

Conclusion: This study of patients with hemiparesis secondary to stroke found that the use of a non-immersive virtual reality smart glove can accelerate improvement in hand strength and function.

Lee, H., et al. Non-Immersive Virtual Reality Rehabilitation Applied to a Task Oriented Approach for Stroke Patients: Randomized, Controlled Trial. **Restor Neurol Neurosci.** 2020: 1-8.

ORAL L-TYROSINE IMPROVES CORE TEMPERATURE MAINTENANCE IN OLDER ADULTS

Advanced age is accompanied by a decline in thermoregulatory responses to cold exposure. To sustain norepinephrine (NE) release and vasoconstriction (VC) of cutaneous vessels during cold stress, sufficient sympathetic nerve firing and an adequate axonal pool of L-tyrosine is required. This study assessed whether supplementation with L-tyrosine would improve cutaneous VC response during whole body cooling.

Subjects were nine young (mean age 25 years) and nine old (mean 72 years) healthy adults, randomized to receive either L-tyrosine (150 mg/kg-1) or placebo. Esophageal temperature and forearm laser Doppler flux (LDF) were measured to provide an index of core temperature (Tc) and skin blood flow. The subjects were placed in a water perfused suit cooled to maintain skin temperature at 34^0C. Esophageal temperature (T_{ES}) was measured with a sterile thermistor, fed through a naris to the level of the heart. The suit was cooled for 90 minutes to 29.5°C. A temperature perception survey was completed at the end of the cooling period.

The T_{ES} at the end of cooling was lower in the older placebo group than in the other three groups ($p < 0.05$). Tyrosine supplementation did not affect thermoregulatory variables in the young ($p > 0.05$). However, in the older adults, tyrosine supplementation attenuated the decline in T_{ES} and the T_{ES} slope, with a lower absolute cutaneous vascular conductance (CVC) by the end of the cooling session ($p < 0.05$). Compared to the placebo group, a reduced perception of the cold with supplementation was found only in the young group ($p= 0.007$).

Conclusion: This study demonstrates that tyrosine supplementation can help elderly individuals maintain core temperature during exposure to cold ambient temperatures.

Lang, J., et al. Oral L Tyrosine Supplementation Improves Core Temperature Maintenance in Older Adults. **Med Sci Sports Exerc.** 2020, April; 52(4): 928–934.

VAGUS NERVE STIMULATION FOR ENHANCED SOMATOSENSORY RESTORATION

As Vagus Nerve Stimulation (VNS) has shown promise in the phasic activation of neuromodulary systems, this animal study assessed the ability of VNS, when paired with tactile rehabilitation, to improve recovery in an animal model of chronic sensory loss.

Adult rats underwent transection of both the median and ulnar nerves. At 15 weeks the animals were randomized to a control group or to undergo a vagus nerve stimulator implantation. Both groups received tactile rehabilitation (Rehab) sessions, 1.5 hours in duration, four days per week for two months. Each session involved 200 presentations of a range of tactile stimuli applied to the ventral surface of the injured paw. In addition, the VNS+Rehab group received a 0.5-second train of VNS paired with the delivery of each stimulus. The animals were tested for mechanosensory withdrawal thresholds, changes in grip strength, forearm asymmetry and horizontal ladder rung testing. The results of these tests were compared between groups.

In both groups, mechanosensory withdrawal was significantly elevated (worsened) eight weeks postinjury, stabilizing at 16 weeks. Compared to the Rehab group, significantly greater improvements in somatosensory thresholds were noted in the VNS+Rehab group beginning during the first week of therapy. This difference was maintained at completion of the last session at week 22 ($p<0.001$) and continuing until week 30 ($p<0.05$). The performance of the VNS+Rehab group was also superior to the Rehab group, as measured by toes spread ($p<0.001$) and fewer misses/slips on the horizontal ladder rung test ($p<0.001$). Motor function did not differ between groups.

Conclusion: This animal study of peripheral nerve transection and repair suggests that vagus nerve stimulation can enhance the efficacy of tactile rehabilitation in restoring the function of the somatosensory system.

Darrow, M., et al. Restoration of Somatosensory Function by Pairing Vagus Nerve Stimulation with Tactile Rehabilitation. **Ann Neurol.** 2020, February;87(2):194-205.

OBESITY AND PATELLOFEMORAL OSTEOARTHRITIS

Cross-sectional studies have shown that patellofemoral (PF) osteoarthritis (OA) is more prevalent among those with a higher body mass index (BMI). However, no studies have shown a longitudinal relationship between obesity and the development of PFOA. The Cohort Hip and Cohort Knee (CHECK) Study is a longitudinal, prospective, observational study of adults who presented with hip and/or knee complaints (pain or stiffness) who had

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not previously visited a doctor for this complaint.

This observational, longitudinal, prospective study followed patients, 45-65 years of age who presented with a complaint of knee pain but had no radiographic evidence of OA of the knee. At baseline and follow up, BMI was recorded, and radiographs taken.

Data were complete for 528 patients. At eight year follow up, compared to those with a normal BMI at baseline, the odds ratio (OR) for developing PFOA was 1.3 for those with a BMI in the overweight range and 1.8 for those with a BMI in the obese range ($p<0.05$). The same relationship was seen between BMI and radiographic OA of the tibiofemoral joint. No significant association was found between percent BMI change over time and the development of PFOA.

Conclusion: This longitudinal study found that obesity is related to the incidence of radiographic positive patellofemoral osteoarthritis.

Hart, H., et al. Obesity Is Related to Incidence of Patellofemoral Osteoarthritis: The Cohort Hip and Cohort Knee (CHECK) Study. **Rheum Int**. 2020 Feb. 40; 227-232.

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