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FEMALE REPRODUCTIVE FACTORS AND DEMENTIA

Evidence suggests that estrogen may have a positive impact on memory, affect, and motor coordination in women. This study was designed to investigate the association between female reproductive factors and the incidence of dementia.

The National Health Insurance Service (NHIS) is the single insurer in Korea, providing medical care to 97% of the Korean population. From the NHIS data 4,775,398 post-menopausal women were identified. Age at menarche and age at menopause were determined, with the duration of fertility calculated as the interval between the two. The number of children and total lifetime history of breast feeding was recorded for each woman. The duration of hormone replacement therapy was categorized as never, less than two years, two-five years or five or more years. The endpoint of the study was newly diagnosed dementia including Alzheimer's disease, vascular dementia or other dementia.

During a median follow-up of 5.74 years, there were 212,227 cases of all-cause dementia. In a dose-dependent manner, the incidence of all-cause dementia increased significantly with later age of menarche, earlier age of menopause, shorter duration of fertility and never users of HRT ($p < 0.001$). This association was noted for both Alzheimer's disease and vascular dementia. Compared to women who experienced menopause before the age of 40 years, those who underwent menopause after the age of 55 years had a significantly lower risk of dementia (HR 0.79). Compared with those who never used HRT, those who had used HRT had a 15% lower risk of dementia. Those who used oral contraceptives had 10% lower risk of dementia compared to nonusers.

Conclusion: This retrospective study of women in South Korea found that later menarche, earlier menopause and shorter duration of fertility were each independently associated with an increased risk of dementia in postmenopausal women.

Yoo, J., et al. Female Reproductive Factors and the Risk of Dementia: A Nationwide Cohort Study. **Eur J Neurol**. 2020, Aug; 27(8): 1448–1458.

POST-TRAUMATIC HEADACHE WITH A CLUSTER PHENOTYPE

A post-traumatic headache is defined as a headache developing within seven days of head trauma. Tension-type headache and migraine without aura are the usual phenotypes. This study assessed the prevalence of post-traumatic cluster-type headaches.

This retrospective cohort study was completed between January of 2007 and May of 2017. Consecutive patients with post-traumatic headaches, diagnosed as cluster headaches, were assessed. Data were collected, including demographic characteristics, attack frequency, duration, laterality and associated symptoms. Patients with post-traumatic headache of a cluster variation (PTH-CH) were compared with controls and with patients with non-trauma related CH.

During the 10 years of the study, 26 patients were identified with PTH-CH. A control cohort included 553 patients with primary CH, without any history of trauma. For the study patients, the mean duration of attacks was 87.3 minutes, with a mean frequency of 3.3 per day. At least one autonomic feature was present during the attacks, with restlessness during the attack reported in all but two patients. There was a distinct circadian periodicity, with the attacks occurring predictably during the night in 24 (92.3%) patients. Compared to controls, those with PTH–CH were more likely to report a parietal location of referred pain, and to report being resistant to preventative treatment. A multivariate analysis revealed a significant, positive association between PTH–CH and a family history of CH, temporal location, parietal location, with symptoms during the attacks including edema, meiosis, rhinorrhea, facial sweating and restlessness. Those with PTH–CH were significantly less likely to present with frontal referred pain.

Conclusion: This case series of patients with post-traumatic headaches of the cluster type found that these patients had a strong family history of cluster headaches, pain predominantly in the temporal or parietal region and autonomic symptoms during the attacks.

Grangeon, L., et al**.** New Insights in Post-traumatic Headache with Cluster Headache Phenotype: A Cohort Study. **J Neurol Neurosurg Psychiatry.** 2020, June; 91(6): 572-579.

THEOPHYLLINE AS AN ADD-ON TO THROMBOLYTIC THERAPY IN ISCHEMIC STROKE

Thrombolysis with intravenous recombinant tissue-type plasminogen activator and endovascular treatment, in cases of large vessel occlusion are considered standard therapies for patients with acute ischemic stroke. As theophylline is thought to be neuroprotective, due to its cerebral vasoactive properties, this study assessed whether theophylline, as an add-on to thrombolytic therapy, is safe and effective for patients with acute ischemic stroke (AIS).

The Theophylline in Acute Ischemic Stroke (TEA-Stroke trial) is a phase II clinical study with a randomized, double blind, placebo controlled design. Subjects were patients with AIS undergoing standard thrombolytic therapy within 4.5 hours of symptom onset, all with a NIHSS of four or greater. The participants were randomized to receive either 10 mL of theophylline or a placebo within 30 minutes after the start of thrombolytic therapy. All subjects were assessed for

demographic characteristics, medical history, laboratory values, medications, physical examination and NIHSS score at baseline and at 24 hours. A modified Rankin Scale (mRS) score at 90 days was used to assess functional outcomes. Brain MRI was performed at baseline and at 24-hour follow-up.

Subjects were 33 patients in the theophylline group and 31 in the control group. At 24 hours, the theophylline group had significantly better NIHSS scores than the control group (p=0.044). Major clinical improvement, defined as greater than 50% improvement in the NIHSS score, was observed in 67% of the treatment group and 45% of the control group (p=0.70). The mean infarct volume at 24-hour follow-up was 17.2 mL for the theophylline group and 24.5 mL for the control group (p=0.762).

Conclusion: This proof of concept trial of theophylline administration added during thrombolytic therapy for acute ischemic stroke did not find a statistically significant positive effect for early clinical improvement in infarct growth, although the small sample size precluded strong conclusions.

Modrau, B., et al. Theophylline as an Add-on to Thrombolytic Therapy in Acute Ischemic Stroke. A Randomized, Placebo Controlled Trial. **Stroke.** 2020, July; 51 (7): 1983-1990.

MESOTHERAPY FOR LOW BACK PAIN

Mesotherapy involves a series of micro-injections in the upper layers of the skin, found to allow for a lower administration of other analgesic medications. This study of patients with back pain compared the efficacy of one session of mesotherapy to that of IV infusion of dexketoprofen.

This prospective, randomized, controlled trial included adults with acute low back pain related to disc herniation. Those randomized to a mesotherapy group received injections of a mixture of one cc (two mg) of thiocolchicoside, one cc (16.2mg) of lidocaine and 1 cc (5mg) of tenoxicam. Injections of 0.1 to 0.2 cc of the mixture were injected at a depth of one to three mm. A minimum of 50 injections were performed from L1 to S1 vertically and within three to four cm left, and three to four cm right, of the processus spinosus horizontally. Those in the systemic group received 50 mg of dexketoprofen, mixed in 100 cc of IV isotonic solution and infused over five minutes. Pain was measured with a visual analog scale (VAS) on admission and up to 24 hours after treatment. The primary outcome measures were change in back pain intensity and the use of analgesics within 24 hours after treatment.

Data were completed for 52 patients in each group. The median durations of pain were four hours in the mesotherapy group and 4.5 hours in the systemic therapy group. Improvement in VAS pain scores from baseline to 15 minutes, baseline to 30 minutes, baseline to 45 minutes and baseline to 24 hours were significantly better in the mesotherapy group (p<0.001 for all). The use of analgesics within 24 hours was three times higher in the systemic group than in the mesotherapy group.

Conclusion: This study of patients with acute low back pain, seen in the emergency department, found that mesotherapy provided superior pain relief than did IV dexketoprofen.

Akbas, I., et al. Comparison of Intradermal Mesotherapy with Systemic Therapy in the Treatment of Low Back Pain: A Prospective, Randomized Study. **Am J Emerg Med.** 2020, July 1;38(7): 1431-1435.

INTRAVENOUS FLUIDS FOR HEADACHES

For patients presenting to the emergency department with a chief complaint of headache, intravenous fluids are provided in approximately 40% of the time. This study examined the efficacy of this treatment for patients with benign headaches.

Subjects were patients, 10-65 years of age, presenting to the emergency department with a chief complaint of headache. After screening for neurologic etiologies, the patients were randomized to receive a fluid bolus of normal saline, run over one hour, of 20 mL/ kg up to 1000 mL (treatment group), or 5 mL/ kg (control group). No rescue medications were given for at least 30 minutes. Prior to the administration of rescue medications, the patients filled out a data collection form including age, sex, race, baseline headache and nausea severity scores, with these repeated at 30 and 60 minutes. The standardized rescue medications offered were prochlorperazine 0.15 mg/kg up to 10 mg intravenous and diphenhydramine 1 mg/kg up to 50 mg intravenous. The main outcome measure was the difference in

median pain score improvement between the treatment and the control groups at 60 minutes.

Of the 58 patients enrolled, 35 were randomized to the fluid bolus group and 23 to the control group. At 60 minutes, the mean pain score dropped by 48.3 mm (on a 100 mm pain scale) in the fluid group and 48.7 mm in the control group (p=0.96). No difference was seen between groups in secondary measures including mean pain score reductions at 30 min, mean nausea score reductions at 30 or 60 min, the percentage who received rescue medications, the percentage who were admitted to the hospital or the percentage of patients who had a headache at 24–48 hour follow-up.

Conclusion: This study of patients presenting to the emergency department with acute headaches found that IV fluids did not assist with pain reduction.

Zitek, T., et al. I-FiBH Trial: Intravenous Fluids in Benign Headaches–A Randomized, Single Blinded Clinical Trial. **Emerg Med J.** 2020, Aug; 37(8):469-473.

HEADACHE WITH CERVICAL DISC DISEASE AFTER SURGERY

Studies have suggested that over 50% of individuals with cervical radiculopathy (CR) experience headache, commonly classified cervicogenic headache. This study investigated the effects of surgery, with either structured postoperative physiotherapy (SPP) or a standard postoperative approach (SPA), on trauma related headaches in patients with CR.

Subjects were patients with CR, scheduled for surgical decompression. The participants were randomized to receive either SPP or SPA. The SPP involved graded, neck-specific exercises, combined with a cognitive behavioral approach, with the goal of improving function and performance of basic activities, increasing self-efficacy and learning strategies for coping with pain and disability.

The SPA group followed usual postoperative care specific for each clinic. The patients were asked to rate headache intensity postoperatively, at six weeks and at months three, six and twelve. A visual analog scale (VAS) was used to rate headaches, including current, at best and at its worst, within the prior week.

Of the 202 individuals in the main study, 106 had preoperative neck related pain and were included in the analysis. From baseline to one year postoperatively, the patients reported improvement in headache ratings of current (p<0.001), worst in the last week (p<0.001) and best in the last week (p<0.001). No difference was seen in outcomes between the two groups. Changes in current headache intensity from baseline were significantly associated with changes in current neck pain intensity (p=0.001).

Conclusion: This study found that 52% of patients with cervical radiculopathy reported headache, which was correlated with neck pain, and was significantly improved after surgical decompression.

Svensson, J., et al. Neck-Related Headache in Patients with Cervical Disc Disease after Surgery and Physiotherapy: A One-Year Follow-up of a Prospective, Randomized Study. **Spine.** 2020, July; 45 (14): 952-959.

ORTHOSTATIC HYPOTENSION AND COGNITIVE FUNCTION IN THE ELDERLY

Orthostatic hypotension (OH) is defined as a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within three minutes of standing. This study assessed the impact of OH on all domains of cognitive function over time in patients 50 years of age or older.

Data were gathered from the Tubingen Risk Evaluation for Neurodegenerative Diseases (TREND), a prospective, longitudinal study initiated in 2009. The subjects were 50 to 80 years of age, all without neurodegenerative disease at baseline. Each participant underwent an extensive assessment battery. Orthostatic function was defined by BP during lying and at after 30, 90, 150 and 210 seconds of active standing. Cognition was assessed with the German version of the extended CERAD-Plus neuropsychological battery. Those with OH were compared to those without.

Of the 495 subjects, 17.6% presented with OH at baseline (OH+). Compared to the OH- subjects, the OH+ cohort obtained poorer CERAD performance scores at baseline (p<0.001) and a more rapid deterioration in scores over time (p<0.001), as well as poorer performance on subtests of memory function. In addition, as compared to the OH- group, the OH+ group produced a higher, average vascular burden index (p<0.001), and demonstrated a higher prevalence of hypertension (p=0.003) and a higher prevalence of obesity (p=0.009).

Conclusion: This study of patients 50 years of age or older found that the prevalence of orthostatic hypotension increases with age and is associated with faster deterioration in cognitive function.

Zimmermann, M., et al. Orthostatic Hypotension as a Risk Factor for Longitudinal Deterioration of Cognitive Function in the Elderly. **Euro J Neurol**. 2020; 27(1): 160-167.

SPREADING DEPOLARIZATIONS AND BRAIN INJURY OUTCOME

Spreading depolarizations are a class of pathological brain waves, triggered by ischemia, trauma or other noxious stimuli. These waves propagate slowly through cerebral gray matter and are characterized by a near-complete, sustained collapse of electrochemical membrane gradients in neurons and astrocytes. This study of patients with traumatic brain injury (TBI) assessed the association between these depolarizations and clinical outcomes.

Subjects were patients with severe TBI requiring neurosurgery, seen within seven days of injury. After surgery, a linear electrocorticography strip was placed on the cerebral cortex near the focus of the primary injury. Electrocorticography was used to detect cortical spreading depressions (CSD). Hospital admission variables were collected for outcome prognostication, as defined by the IMPACT study. Associations were noted between CSDs and clinical outcome (as measured by Glasgow Coma Scale's Outcome Scale-E (GOS-E) measures).

The final cohort comprised 138 patients, of whom 78 had sustained cerebral contusions and 73 subdural hematomas. During the study, CSDs were recorded in 83 of 138 patients. A multivariate regression analysis found that the finding of depolarization clusters was associated with a significantly worse clinical outcome, with an odds ratio of 2.29 (p=0.02). The odds ratios for poorer outcomes were 1.17 (p=0.70) for those with sporadic CSDs, 2.43 (p=0.04) for those with clustered CSDs and 2.13 (p=0.10) for those with isoelectric SDs.

Conclusion: This study of patients with severe traumatic brain injury found that spreading

depolarizations, especially in clusters, are associated with poorer functional outcomes.

Hartings, J., et al. Prognostic Value of Spreading Depolarizations in Patients with Severe Traumatic Brain Injury. **JAMA Neurol.** 2020, April; 77 (4), 489-499.

TOCOPHEROL AND DOXYCYCLINE FOR BRAIN INJURY

In traumatic brain injury (TBI), altered blood brain barrier permeability and cellular inflammation combine to enhance the generation of an excess of reactive oxygen species, reduce mitochondrial function and activate processes that result in apoptosis. This study reviewed the mechanism of tocopherol and doxycycline as a neuroprotective agent in animals with TBI.

This animal study included healthy, male rats with induced TBI. One group without brain injury served as a control group. At seven days post-TBI, the rats were trained in a Morris Water Maze, an open field, measured for grip strength, and object recognition. After training, the subjects were randomized into groups of seven to receive: a) placebo, b) doxycycline 50 mg/kg, c) doxycycline 100 mg/kg, d) tocopherol 5 mg/kg, e) tocopherol 10 mg/kg, f) doxycycline 50 mg/kg plus tocopherol 10 mg/kg. On the 29th day of the study, the animals were sacrificed to allow for testing of biochemical, neuroinflammatory and neurotransmitters.

Locomotor activity was significantly improved with both doses of doxycycline and both doses of tocopherol, as well as the combination of these treatments ($p<0.01$-$p<0.001$). Both doses of both drugs improved grip strength, with the combination group recovering grip strength significantly better than the other groups($p<0.01$-$p<0.001$). The same pattern was found for escape latency, the target quadrant test, and for recognition memory, oxidative stress parameters and inflammatory markers.

Conclusion: This animal study of induced traumatic brain injury found that doxycycline and tocopherol improved memory and function, and that this improvement is associated with improved neuro-inflammatory, biochemical and neurotransmitter processes.

Rana, A., et al. Pharmacological Potential of Tocopherol and Doxycycline against Traumatic Brain Injury-Induced Cognitive/Motor Impairment in Rats. **Brain Inj.** 2020, July; 34 (8):1039-1050, DOI: 10.1080/02699052.2020.1772508

POST-STROKE, DIRECT ANTICOAGULATION AND ATRIAL FIBRILLATION

Studies have indicated that the direct oral anticoagulants (DOACs) are as effective as vitamin K antagonists for the anticoagulation treatment of patients with atrial fibrillation (AF). The initiation of DOACs in these studies is often delayed until seven to 30 days, due to concern regarding hemorrhage into the infarcted tissue. This study investigated the efficacy of early initiation of DOACs and vitamin K antagonists (VKA) in patients with AF following ischemic stroke.

Data were obtained from the Early Initiation of Direct Anticoagulation after Stroke in Patients with AF (EIDASAF) study. Subjects were 18 years of age or older, each with AF and treated at the Hyper Acute Stroke Unit of the Imperial College Healthcare NHS Trust between 2010 and 2017. Data of consecutive patients were extracted including the severity of the index stroke, the choice of anticoagulants and the timing of the initiation of anticoagulation. The primary outcome variable was major bleeding, defined as fatal and/or symptomatic bleeding in a critical area or organ, and/or a fall in hemoglobin level of 20 g/L. Documentation also included the rates of ischemic cerebrovascular events and mortality.

Data were analyzed for 959 consecutive patients with AF and ischemic stroke, with a mean treatment onset of seven days and a mean follow-up of 16.1 days. The rates of any major bleeding were three percent in those treated with any anticoagulant, as compared with 4.4% in the no treatment group ($p=0.106$). Treatment with any DOAC ($p= 0.043$) but not with a VKA ($p=0.632$) decreased the odds of major bleeding compared with no anticoagulation. The risk of recurrent stroke or TIA during the inpatient stay did not significantly differ between the anticoagulated group and the non-anticoagulation group ($p=0.522$).

Conclusion: This non-randomized study of patients with atrial fibrillation, hospitalized with ischemic stroke, found that initiating anticoagulation with direct oral anticoagulants, after a mean of seven days, did not increase the risk of major bleeding.

D'Anna, L., et al. Early Initiation of Direct Anticoagulation after Stroke in Patients with Atrial Fibrillation. **Euro J Neurology**. 2020. doi-org.proxy.library.emory.edu/10.1111/ene.14396.

NORDIC WALKING AND DISTAL RADIAL BONE DENSITY

Nordic walking (NW) was first described in Scandinavia as a Nordic ski training method in 1930. This technique uses hand-held poles to push off during gait. This study analyzed the effects of a six-month program of NW on the bone mineral content of the distal radius.

Subjects were 41, healthy, female college students, randomized to either a NW group or a control group. The students began NW sessions for 30 minutes three times a week, progressing by five to 10 minutes each month for six months. All were assessed at baseline and at follow-up for bone mineral density (BMD) using a dual energy x-ray absorptiometry (DXA), and for muscle cross-sectional area and bone mineral content (BMC).

At follow-up, compared with controls, BMC was significantly improved in the NW group when measured at the distal 1/10 of the radius, but not when measured at the distal 1/6 or the distal 1/3. The same pattern was found for BMD. No significant differences were noted in changes during the study in muscle cross-sectional area or adipose.

Conclusion: This study found that Nordic walking, 30 to 60 minutes per day, three times per week, improved bone mineral density and bone mineral content at the ultra-distal radius.

Kato, T., et al. Nordic Walking Increases Distal Radius Bone Mineral Content in Young Women. **J Sports Sci Medi.** 2020, May; 19: 237-244.

EXTRACORPOREAL SHOCK WAVE THERAPY FOR KNEE ARTHRITIS

Extracorporeal shock wave therapy (ESWT) is often used to help relieve pain in patients with musculoskeletal disorders. In addition, animal studies have suggested that ESWT may have chondral protective effects. This study was designed to better understand

the effect of radial ESWT for patients with symptomatic osteoarthritis (OA) of the knee.

Subjects were patients seen in an outpatient clinic, each diagnosed with knee OA. The participants were randomized to receive ESWT or sham ESWT. For ESWT, patients received 2000 pulses of shockwave at 2.0 to 3.0 bar weekly for three weeks. Both groups received a hot pack, applied to the knee for 40 minutes, and transcutaneous electrical nerve stimulation for 30 minutes, once per week for three weeks. In addition, all were instructed to complete a home-based exercise program for 30 minutes per day for three weeks. Assessments were performed at baseline, at the end of treatment, and at one and three months by a clinician held blind to the treatment group. Assessment tools included a visual analog scale (VAS) for pain and the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC).

Compared to the sham group, the treatment group demonstrated significantly greater improvement at three months in VAS pain scores at rest ($p<0.001$) and during activity ($p<0.001$), as well as during a 20 m walk test ($p<0.001$). The WOMAC pain scores were significantly more improved in the treatment group at three months ($p<0.001$). The WOMAC function scores showed the same pattern as did WOMAC pain scores. In addition, the treatment group demonstrated significantly better improvement than the control group in quadriceps strength through three months.

Conclusion: This randomized, controlled trial involving patients with osteoarthritis of the knee found that weekly radial extracorporeal shock wave therapy improved pain and function, with continued effects measured at three months.

Uysal, A., et al. Effects of Radial Extracorporeal Shockwave Therapy on Clinical Variables and Isokinetic Performance in Patients with Knee Osteoarthritis: A Prospective, Randomized, Single Blind and Controlled Trial. **Intern Ortho**. 2020, July (7): 1311-1319.

FOOT WORN BIOMEDICAL DEVICE FOR KNEE OSTEOARTHRITIS

Symptomatic knee osteoarthritis (OA) is influenced by both biomechanical and neuromuscular events. An adjustable orthotic device (the AposSystem) allows alterations in the foot vector pressure, and thus the knee vectors, and the training of neuromuscular control. This study investigated the clinical efficacy of this device in patients with OA of the knee.

This retrospective chart review included 455 patients with symptomatic OA, with a mean age of 61.6 years. All participants completed a computerized gait analysis and validated PROM at the initial consultation and then at three and six months. The OptoGait system was used to measure spatial-temporal gait parameters while walking barefoot at a self-selected walking speed. All subjects were assessed with the WOMAC scale and a visual analog scale for pain. After the patients completed baseline measurements, the biomechanical devices were individually calibrated to change the foot's center of pressure during gait, in order to reorient vectors so as to reduce loads on the affected joint while walking.

At six months, gait velocity, step length and single-hand cane support of the more symptomatic knee improved significantly ($p<0.001$). In addition, significant improvements were noted in pain, function and quality of life ($p<0.001$ for all). Following six months of treatment, all patients' self-evaluation questionnaires improved significantly. The WOMAC subscales significantly improved following three months of treatment, with further improvements at six months ($p < 0.001$). WOMAC pain scores improved by 48.6%. A significant relationship was found between the changes in gait parameters and the changes in questionnaire results ($p<0.05$ for all).

Conclusion: This retrospective study of patients with osteoarthritis of the knee found that an orthotic device which personalized changes in the foot's center of pressure to shift load vectors in the knee produced significant changes in gait, correlated to significant improvement in symptoms.

Miles, C., et al. The Effect of Treatment with a Noninvasive Foot Worn Biomechanical Device on Subjective and Objective Measures in Patients with Knee Osteoarthritis-A Retrospective Analysis on a U.K. Population. **BMC Musculoskelet Disord.** 2020; 21: 386.

TRENDS IN MENISCAL SURGERY

Among patients with an anterior cruciate ligament (ACL) tear, damage to the meniscus is an important factor for predicting long-term outcomes following ACL repair. Meniscus tears are commonly addressed during ACL reconstruction, with either resection or repair. This study reviewed the incidence of meniscus repairs during ACL repair or in isolation.

Data were retrieved from the Pearl Diver Patient Record Database of patients insured by Humana between the years 2010 and 2015. The database was queried using current procedure terminology (CPT) codes for surgery involving the meniscus with or without an ACL repair. These patients were grouped as those undergoing an isolated discectomy, isolated meniscus repair, isolated ACL repair, meniscus repair combined with ACL repair or meniscectomy combined with ACL repair. The total number of patients seen and the relative number in each category were calculated.

Of those undergoing ACL reconstruction, 18.6% also underwent meniscus repair and 54% underwent meniscectomy. The incidence of isolated meniscectomies and isolated ACL repairs decreased across the study period ($p=0.0230$ and $p=0.0493$, respectively), while the incidence of isolated meniscus repairs remained the same ($p=0.3$). The incidence of meniscectomy combined with ACL repair decreased over time, while the incidence of meniscus repair combined with ACL reconstruction increased over time ($p=0.001$).

Conclusion: This study found that the incidence of isolated meniscectomies had decreased over time, while isolated meniscal repairs remained constant. Over half of all ACL repairs involved either a meniscal repair or a meniscectomy.

DeFroda, S., et al. Trends in the Surgical Treatment of Meniscal Tears in Patients with and without Concurrent Anterior Cruciate Ligament Tears. **Phys Sports Med.** 2020, May; 48(2): 229-235.

HOOKWORM TREATMENT FOR MULTIPLE SCLEROSIS

The hygiene hypothesis postulates that certain infectious agents, including helminths, can protect against inflammatory diseases including multiple sclerosis (MS). *Necator americanus* is a hookworm infecting humans, which can induce a mixed peripheral T-helper cell response. This study examined the effect of hookworm treatment on relapsing MS.

Subjects were clinically stable patients, 18-64 years of age, with relapsing remitting MS or secondary progressive MS. The patients were randomized to a placebo or to a treatment group. The treatment group underwent experimental infection with 25 *Necator americanus* third-stage larvae (L3), by placement on a gauze pad, then applied to the arm. Arrival in the gastrointestinal system was verified by fecal sampling. The placebo group underwent a similar appearing protocol. The patients were assessed clinically with monthly Expanded Disability Status Scale (EDSS) scores through month ten, and Multiple Sclerosis Functioning Composite Scores at baseline and at nine months. Adverse events were recorded at each visit.

Data were available for 66 patients in the treatment group and 34 in the placebo group. At nine months, 87% of the treatment group and 31% of the placebo group had no MRI changes. From baseline to month nine, an increase was noted in the CD4+CD25 ^{high} CD127 ^{neg} T cell percentage from total CD4+Tcells in the treatment group while a decrease was found in the placebo group (p =0 .01). Relapses of MS occurred in 11.4% of the treatment group and in 27.8% in the placebo group. There were nine adverse events in seven patients, including five in the placebo and two in the treatment group.

Conclusion: This study of patients with relapsing multiple sclerosis found that treatment with a hookworm could decrease the number of relapses.

Tanasescu, R., et al. Hookworm Treatment for Relapsing Multiple Sclerosis. A Randomized Double-Blind Placebo Controlled Trial. **JAMA Neurol**. 2020. doi:10.1001/jamaneurol.2020.1118.

NEUROMUSCULAR ELECTRICAL STIMULATION PRESERVES LEG LEAN MASS IN GERIATRIC PATIENTS

Age-related muscle mass loss is associated with poor mobility, loss of independence and increased mortality. 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 with muscle scans, muscle biopsies and tests of muscle function. The intervention involved daily, 30-minute E-Stim sessions of the m. vastus lateralis and the m. vastus medialis muscles of one leg (E-Stim). The contralateral leg served as a control leg (CON). Stimulation intensity 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 between the two legs were noted on tests of muscle power, torque or muscle fiber size. Compared with the CON leg, E-stim resulted in the down regulation of several atrophy signaling pathways and an upregulation of connective tissue and cellular remodeling processes.

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

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

EFFECTIVENESS OF COOLANT SPRAY FOR ANKLE TRAUMA

For musculoskeletal injuries, cryotherapy has been shown to be effective in alleviating pain and ensuring a patient's rapid return to normal activity. This study of patients with acute ankle injuries assessed the clinical value of a coolant spray for those undergoing radiographic procedures during an emergent care evaluation.

Subjects were 160 patients presenting to the emergency room with acute ankle trauma. Participants were randomized to receive either a placebo or a coolant spray. Ten minutes after applying the spray, radiographic examinations were conducted for both groups. Pain scores were obtained, and radiographic imaging results were evaluated for quality by a blinded observer.

The mean quality scores of the radiographic imaging results were 8.13 for patients treated with coolant and 6.58 for patients treated with placebo (p=0.000), suggesting better ability to position, and to sustain the position, during the filming process. The proportion of patients requesting analgesic drugs was significantly higher in the normal saline group than in the coolant group (p=0.025).

Conclusion: This study of patients with acute ankle injuries found that the use of coolant spray (cryotherapy) allowed for better tolerance, thus, better radiographic imaging, with patients requesting fewer analgesic drugs at discharge.

Gur, S., et al. Comparison of Effectiveness of Coolant Spray and Placebo in Patients with Acute Ankle Trauma: Prospective, Randomized, Controlled Trial. **Am J of Emerg Med**. 2020, July; 38(7): 1458-1462.

NEUROMUSCULAR TRAINING TO REDUCE SPORTS INJURIES

While childhood physical activity promotes healthy growth and development, participation in any physical activity must be balanced with the risk of injury. This study assessed the efficacy of a neuromuscular training (NMT) program for reducing injuries in junior high school athletes.

This trial included 12 junior high schools with students ages 11 to 16 years. These schools were randomized to an intervention group, or a control group. For both groups a 15-minute warmup program was delivered by the physical education teacher at the start of each class. The NMT program included aerobic, agility, strength and balance exercises. The control program included aerobic, static and dynamic stretching exercises. An injury surveillance system was used to assess baseline, exposure and injury data. The primary outcome measure was any injury sustained during a sport or recreational activity, which resulted in missed time from the activity or that required medical attention.

During the year of follow-up, there were 69 injuries in the control group and 54 in the NMT group. A regression analysis demonstrated that the intervention program was protective of all reported injuries in girls, but not in boys. In a separate analysis the NMT program was also found to be protective of lower extremity injuries and medically treated injuries, though again, only in girls.

Conclusion: This large, randomized, controlled trial assessing a neuromuscular training warmup program for junior high students found that, compared to controls, the program resulted in fewer injuries, but only among girls.

Emery, C., et al. Implementing a Junior High School-Based Program to Reduce Sports Injuries through Neuromuscular Training (iSPRINT): A Cluster Randomized, Controlled Trial (RCT). **Br J Sports Med.** 2020, August; 54: 913-919.

PHARMACOLOGIC TREATMENT FOR TOBACCO ABUSE

Tobacco dependence remains a pervasive clinical problem in the United States. This paper reports on the official clinical practice guidelines for tobacco cessation, approved by the American Thoracic Society in 2020.

A panel formed by the American Thoracic Society was charged with upgrading the guidelines for clinicians to address tobacco cessation for their patients. A literature search was conducted for relevant studies completed through October 2019. From a review of these, the recommendations were created.

The guideline panel formulated five strong recommendations. These include: 1) for tobacco dependent adults, varenicline was recommended over a nicotine patch, 2) for tobacco dependent adults, varenicline was recommended over bupropion, 3), for tobacco dependent adults, varenicline was recommended over a nicotine patch in patients with a comorbid psychiatric condition, 4) for tobacco dependent adults who are not ready to discontinue tobacco abuse, clinicians should begin treatment with varenicline, and 5) using controller medications for an extended treatment duration greater than 12 weeks. Two conditional recommendations included: 1) combining a nicotine patch with varenicline rather than using varenicline alone and 2) using varenicline rather than electronic cigarettes.

Conclusion: This paper reports on the official American Thoracic Society's clinical practice guidelines for tobacco cessation, including five strong and two conditional recommendations.

Leone, F., et al. Initiating Pharmacologic Treatment in Tobacco -Dependent Adults: An Official American Thoracic Society Clinical Practice Guideline. **Am J Resp Critical Care Med.** 2020, July 15; 202(2): E5-E31.

PLATELET RICH PLASMA FOR ROTATOR CUFF TEARS

Given the poor self-repair capability of the rotator cuff tendons, and the limitations of current surgical interventions, there has been an increased interest in the therapeutic use of platelet rich plasma (PRP). However, given the variability among different PRP preparations, the clinical efficacy of PRP for rotator cuff tendon repair remains unclear. This literature review and meta-analysis was designed to better understand the effect of this intervention.

A literature review was completed to identify studies which assessed PRP as a therapeutic intervention for rotator cuff tears. From this review, 17 level one studies were chosen, involving 1,116 patients. Of these, 545 were treated with PRP. Outcome measures included the Constant-Murley (Constant) score, a visual analog scale (VAS) score for pain, the re-tear rate, the Simple Shoulder Test (SST) and the American Shoulder and Elbow Surgeons (ASES) score.

The meta-analysis found that patients who received PRP demonstrated improvement in Constant scores, both short-term and long term ($p<0.01$ for both). Improvements in VAS pain scores were significant in the short-term ($p<0.01$). Patients who received leukocyte-rich PRP had significantly better Constant scores than did those receiving leukocyte-poor PRP. The long-term odds of re-tears were decreased in those receiving leukocyte poor PRP (OR 0.36) as well as leukocyte rich PRP (OR 0.32), with all significant at $p<0.05$.

Conclusion: This meta-analysis of studies addressing rotator cuff tears found that platelet rich plasma improved functional outcome and pain, while reducing the long-term odds of a recurrent tear.

Chen, X., et al. Use of Platelet Rich Plasma for the Improvement of Pain and Function in Rotator Cuff Tears. **Am J Sports Med**. 2020, July; 48 (8): 2028-2041.

SLEEP DISRUPTION AFTER BRAIN INJURY AND FUNCTIONAL RECOVERY

Complaints of sleep disturbance have been recorded in up to 70% of patients after a brain injury. There is little research to indicate whether sleep quality during the rehabilitation period correlates with outcome or change in function over time. This study examined the relationship between sleep quality and outcome measures.

This prospective, observational study included hospitalized patients with acquired brain injury who required rehabilitation. Sleep quality and motor assessments were conducted at admission, at midpoint of the stay, and prior to discharge. For a control group (CON), sleep quality was assessed for 55, age and gender-matched, community dwelling, healthy adults. Sleep quality was assessed through actigraphy, using a motion watch and a sleep condition indicator. Subjects were also assessed with the Hospital Anxiety and Depression scale (HADS). Motor assessments were performed using the Action Research Arm Test (ARAT) and functional independence was measured with the functional independence measure (FIM). The participants were also assessed with the Wake After Sleep Onset (WASO).

Sleep duration did not differ between groups. Compared with the CON group, inpatients had more fragmented sleep ($p<0.001$), had higher WASO scores ($p<0.001$) and reported worse subjective sleep quality ($p<0.001$). Worse HADS scores were associated with worse subjective sleep quality. Those with more time awake during the night had worse ARAT scores ($p<0.001$). In a stepwise linear regression, sleep fragmentation was the only variable found to explain the variance in the rate of change in FIM ($p=0.027$), whereby more disrupted sleep was associated with slower recovery.

Conclusion: This study of patients hospitalized for acquired brain injury found that impaired sleep quality is associated with worse motor outcomes and slower functional recovery.

Fleming, M., et al. Sleep Disruption after Brain Injury is Associated with Worse Motor Outcomes and Slower Functional Recovery. **Neurorehab Neural Repair**. 2020; 34(7): 661-667.

RESISTANCE TRAINING AND MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is defined as a cognitive decline greater than expected for an individual's age and education which does not interfere notably with activities of daily life. As studies have shown that exercise may promote neuroplasticity and promote various neuroprotective mechanisms, this literature review investigated the effects of resistance training on the cognitive function of patients with MCI.

A literature search was completed to identify randomized, controlled trials evaluating the effects of exercise on cognition in patients with MCI. From this search, seven trials were selected, involving 281 patients. The frequencies of training for the

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studies ranged from two to three times weekly, with sessions ranging from 40 to 75 minutes. Training duration varied from three to six months. Each study included an assessment of general cognitive function or of a subdomain of general cognitive function.

The pooled analysis revealed a significant association between resistance training and cognitive function ($p=0.04$), as well as executive function, as compared to findings for controls ($p= 0.003$). The subgroup analysis indicated that patients who exercised twice a week ($p=0.001$) and for greater than 60 minutes per session ($p<0.0006$) exhibited significant improvement in performance, while those who exercised three times a week and at less than 60 minutes per session did not.

Conclusion: This data review and meta-analysis found that resistance training can improve cognition in patients with mild cognitive impairment.

Zang, L., et al. Meta-Analysis: Resistance Training Improves Cognition in Mild Cognitive Impairment. **Int J Sports Med**. 2020. doi.org/10.1055/a-1186-1272.

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